FACILITY AUTOMATION MANAGEMENT ENGINEERING SYSTEMS
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Thursday, 6 May 2004

Documents Management Branch [**HFA-305**]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 03D-0394

FORMAL COMMENTS ON:

"Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment [*G:\5831dft.doc 10/27/03*]."

Pursuant to a "request for comment" in ***FEDERAL REGISTER*, Vol. 68**, **No. 216**, pp 63109 – 63110.

ADDENDUM TO FRIDAY, 30 APRIL 2004 SUBMISSION

BACKGROUND

A review of the Product Quality Research Institute (PQRI) 'recommendation' on which this guidance is based was submitted, on 25 September 2003, to CDER's Ombudsman, Warren Rumble, (via e-mail: **ombudsman@cder.fda.gov**) and, on 30 September 2003, to Dr. Ajaz Hussain, Deputy Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services (via e-mail: **hussaina@cder.fda.gov**).

On 15 November 2003, **FAME Systems** provided comments to this docket based on that review and an in-depth reading of the FDA's **"Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment** [*G:\5831dft.doc 10/27/03*]."

That review added elements that connect various issues in the Draft provided by the Agency to current good manufacturing practice (CGMP), in general, and the drug CGMP and other regulations with which this guidance is required to be congruent.

On 21 January 2004, **FAME Systems** provided a revised Draft Guidance, "**Guidance for Industry — Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Content Uniformity**" *after further review of the FDA's Draft and after in-depth discussions with Jon E. Clark*.

FAME Systems provided this revised guidance document to the Agency because the Draft provided by the Agency was clearly at odds with the fundamentals of CGMP, the clear strictures of **21 CFR Part 210** and **21 CFR Part 211**, and many aspects of sound inspection science.

To complete the comment process, **FAME Systems**:

- Has reviewed the formal comments, other than those submitted by **FAME Systems**, available electronically in Public Docket 2003D-0493 as of 1 April 2004 by those who commented against the fundamentals of CGMP, the clear strictures of **21 CFR Part 210** and **21 CFR Part 211**, and the basic precepts of sound inspection science.

- Submitted a scientific and CGMP-conformance assessment of those formal comments on 30 April 2004.
- Is submitting this follow-on review of the PDA's comment published to the e-Docket on 15 April 2004.

To clearly separate **FAME Systems'** review statements from the formal comments of those who submitted such, the review comments are in an **Arial** or ***italicized Arial*** font and the original commenters' submissions are in a **Times New Roman** or the other fonts used by the commenters.

In general, the available formal comments were reviewed by the Agency's posting category, "C" or "EMC," and then in the order they were posted to the docket.

For simplicity, each commenting firm or group was addressed in the singular even when the comments are clearly from multiple persons.

When either a binding regulation or a statute is quoted, the text is in a **Lydian** font.

When other recognized sources are quoted, a **Perpetua** font is used.

Should anyone who reads this review find that its guidance is at odds with sound inspection science or the applicable CGMP regulations, or that additional clarification is needed in a given area, then, in addition to providing the sound science or rationale that refutes the review text provided, or his or her clarifying comments to the public docket, he or she is asked to e-mail **drking@dr-king.com** a copy of that sound science, rationale, and/or commentary.

Respectfully,

Dr. King

C-12 Comments By PDA, An International Association for Pharmaceutical Science and Technology, Submitted 5 April 2004 and Posted 15 April 2004

The PDA begins by stating:

"PDA is pleased to provide these comments on the FDA Draft Guidance for Industry on "Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment". PDA is an international professional association of more than 10,500 individual member scientists having an interest in the fields of pharmaceutical science, manufacturing and quality. Our comments were prepared by a committee of experts in the field. These stakeholders are ready to work with FDA via PDA to further develop and refine the guidance for Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment that would ensure quality products in the market place, which is the ultimate goal of both FDA and industry.

We are pleased to offer our comments in order to further improve the document. We trust that our comments will be received as they were intended; that is, to strengthen the utility of the guidance that will be used by people with very diverse needs: ORA, Compliance, OPS, and the regulated industry."

The PDA's reviewed comments are as follows:

"Of particular note are the following recommendations:

1) The PQRI report to the FDA recommended the exclusion from the requirements of the guideline those products where the determination of dosage-form uniformity by weight variation is allowed. The former draft BU guidance for ANDA products also excluded these products. If they are not excluded, it is recommended that the Agency reassess the economic impact to the industry of the additional burden of now running both potency and weight variation analysis on these products."

> Apparently, those who crafted the "PQRI report to the FDA" made their recommendations with little or no comprehension of either the CGMP ***minimums*** or what needs to be assessed in a non-discrete material, or the dosage units formed from it, to comply with the clear requirement *minimums* set forth in **21 CFR 211.110**.
>
> This is the case because the CGMP regulations ***require,*** *for each batch of all drug products*: **a)** the sampling and testing of *batch representative samples* at each *significant phase* during the manufacture of a batch (**21 CFR 211.160(b)(2)** and **21 CFR 211.110(c)**, **b)** the setting of *specifications appropriate to* acceptance of the batch based on the results found from the testing of each ***representative sample*** *of* the *batch at each significant phase* (**21 CFR 211.110(b)**), **c)** the testing of a ***representative sample*** from the *batch* at each significant phase during manufacture for all critical variable factors that may adversely impact the uniformity of the in-process material and the drug product (**21 CFR 211.110(a)**), **and d)** *the release* or rejection of *each batch* at *each significant manufacturing phase by* the manufacturer's *quality control unit* (**21 CFR 211.110(c)**).
>
> There is no valid sound science that would support <u>not</u> assuring that such drug products are adequately uniform before they are released *because there will be no post-release evaluations* – don't assure uniformity because the post-release **USP** requirements do <u>not</u> check for active uniformity – an approach that is <u>not</u> only anti-quality and illegal but also ignores the need for the assessment of the uniformity of each "mix" for *other critical variable factors*.

The applicable "**WEIGHT VARIATION**" subsections, "UNCOATED AND FILM-COATED TABLETS," and "HARD CAPSULES," end the same way, "**assuming homogeneous distribution of the active ingredient.**"

When the **USP** permits homogeneity to be assumed, it is more important that the pre-release testing assure that the **USP**'s post-release assumption condition is met than when the post-release **USP** testing requires a content uniformity determination.

Further, in 1998, the US Supreme Court held that the Agency has no latitude (discretion) with respect to issuing any written statement that conflicts with the ***clear*** requirements of any binding CGMP regulation.

Recognizing this compliance deficiency in the "former draft BU guidance for ANDA products," the Agency properly corrected it in this draft guidance.

For all of the reasons cited, this reviewer recommends that PDA's remarks here be rejected by the Agency because they clearly conflict with both sound inspection science and the law.

"2) The guidance avoids the term 'Validation' and uses less descriptive titles like 'verification of manufacturing criteria.' The PDA feels that the reluctance to use the term 'Validation' creates a disconnect with the PQRI proposal and makes the Guidance more difficult to interpret.

Charged with drafting guidance that agrees with the clear requirements of the applicable CGMP regulations and conforming to: **a)** the Agency's understanding thereof and **b)** Agency policy, the draft does not, as the commenter asserts, avoid using "the term 'Validation'" because, by this reviewer's count, the word "validation" appears eight (8) times in the body of the Draft so it is less than fair to claim that those who drafted this guidance either "avoids the term" or are reluctant "to use the term 'Validation'."

Based on the commenter's recommendation, it would seem that the commenter's real concern is that the titles do not use the terms "development" and "validation" when, in light of the recent revisions to FDA **CPG 7132c** in **Sec. 490.100**, "Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08)," official as of 12 March 2004, this commenter should realize why the Agency avoided the use of the term "validation" in the titles of the sections in this drug product[1] guidance. Moreover, because this guidance is intended to apply generally, it is inappropriate to use the word "development" in the section titles because that word carries with it the connotation of an activity limited to new products when it is actually guidance applicable to all products.

Based on the definition of validation in the recently issued FDA policy, CPG 7132c, ALL such "drug product" batches are "validation" batches as per **21 CFR 211.110(a)**'s "control procedures shall be established to monitor the output and to validate the performance of

[1] **21 CFR 210/3(b)(4)**, "(4) Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo."

those manufacturing processes that …" for each batch and its use to differentiate between phase would, *in light of this policy and the cited regulation*, be futile.

Under **21 U.S.C. 321g(1)**, *that defines a drug*, all "development" batches that are administered to humans or animals are drug product batches upon which firms must use control procedures "to monitor and validate …" as per **21 CFR 211.110**.

"The term 'Validation' is well defined by the Industry and the FDA and the term should be utilized to denote those activities in this guidance that clearly fall under its purview."

Based on the preceding realities, it would seem that, while the term "Validation" is well defined by the FDA (**see CPG 7132c.08** [effective March 12, 2004] that addresses the Agency's current views in process validation requirements in Sec. 490.100, titled "**Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval** (CPG 7132c.08),") in a manner that clearly agrees with the in-process CGMP regulations' "each batch," journey view as set forth in **21 CFR 211.110(a)** and based on that clear definition the draft's decision not to use the term "Validation" more than the eight (8) times it did seems most appropriate. [**Note:** *With emphases added by this reviewer* Sec 490:100 states, "**Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110)**, and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. *A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. The* ***proof of validation is obtained*** *through rational experimental design and the evaluation of data*, preferably **beginning *from* the process development phase** and **continuing *through* the commercial production phase**."]

Further, based on the FDA's definition, it would seem that the PDA and some in the Industry apparently do not, *contrary to the PDA's statement*, seem to understand the scope and import of this "well-defined" term.

Based on all of the preceding, it would seem that, if anything, the Draft overused the term "Validation" and the titles used in the Draft correctly used a more appropriate word.

"PDA would like to praise the cooperative effort between Industry and the FDA via PQRI that has resulted in the utilization of good science and logic to bring resolution to an area of some controversy and disagreement. The resultant benefactor of this Guidance will be the consumer, who now can be assured of the efficacy of their medication."

Based on this reviewer's in-depth review of the original draft guidance and the comments provided by the others who commented to the docket before its comment closing date of 8 March 2004:

A. The draft guidance is bereft of sound science,

B. Falsely equates:

biased non-representative sample active uniformity assessment, *at a confidence level of less than 20 %*, of the output from only the (final) blend and dosage-unit phases

with

unbiased *representative sample* overall (*for the variability of **all** critical characteristics that may affect the uniformity of the in-process materials and the drug product*) uniformity assessment, *at a confidence level that is not less than 95 %*, of the output from "each significant phase" during manufacture,

C. Ignores recognized consensus standards for batches of discrete units, including the recognized consensus standards, **ANSI/ASQC Z1.9**-1993, "**SAMPLING PROCEDURES AND TABLES FOR INSPECTION BY VARIABLES FOR PERCENT NONCONFORMING**," American Society for Quality, (ASQ), 611 East Wisconsin Avenue, P.O. Box 3005, Milwaukee WI 53201-3005, USA, Tel.: 1-800-248-1946 Ext 7244 or 1-414-272-8575 (or its ISO equivalent, ISO 3951:1989), that set forth (*at the 95 % confidence level*) sampling plans that CLEARLY establish the minimum number of *tested **representative** samples* whose valid results can be used to *scientifically* predict whether or not the untested majority of "each batch" is, *or is NOT*, acceptable (as a manufacturer **must** do), **and**

D. Fails to comply with the clear applicable CGMP requirement minimums set forth in 21 CFR Part 211.

"PDA would be pleased to offer our expertise to assist in the clarification of our comments, and the continued evolution of this important guidance. We look forward to working with FDA, industry and other professional associations to develop a world-class guidance document."

Based on a dissenting view in an "accepted then refused" "Letter to the Editor"[2] *concerning the PQRI's "recommendation" that the PDA refused to publish even though they had no problem publishing the PQRI's "recommendation" attest*, the PDA seems to be closed to dissenting views.

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[2] The letter submitted, accepted, and then rejected, stated:

Dear Sir:

The articles, "The Use of Stratified Sampling of Blend and Dosage Units To Demonstrate Adequacy of Mixing For Powder Blends" (Volume 57(2), 2003) and "The Compliance and Science of Blend Uniformity Analysis" (Volume 55(4), 2001) do not fully address, much less comply with, the fundamental legally binding CGMP requirements set forth in 21 CFR 211, including the fundamental mandate for representative sampling (21 CFR 211.160(b)).

In addition, for dosage units, their "inspection plans" are not scientifically sound and fail to recognize, much less consider, the recognized standard ISO 3951 (or, its American equivalent, ANSI/ASQC Z 1.9) that establishes the minimum scientifically sound inspection plans for batches of discrete entities at the 95 % confidence level.

Further, these articles ignore the in-process CGMP requirements set forth in 21 CFR 211.110, Sampling and testing of in-process materials and drug products, that states (bolding emphasis added):

"(a) **To assure batch uniformity** and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and **tests**, or examinations to be conducted **on appropriate samples of in-process materials of each batch**. Such control **procedures shall** be established to **monitor** the **output and** to **validate** the **performance of** those manufacturing **processes** that may be **responsible for** causing **variability in** the **characteristics** of **in-process**

material and the drug **product**. Such control procedures shall include, but are not limited to, the following, where appropriate:

1) Tablet or capsule **weight variation**;
2) **Disintegration** time;
3) **Adequacy of mixing to assure uniformity** and **homogeneity**;
4) **Dissolution** time and rate;
5) Clarity, completeness, or pH of solutions.

(b) **Valid in-process specifications for such characteristics shall be** consistent with drug product final specifications **and shall be** derived from previous acceptable process average and process variability estimates where possible and **determined by** the **application of** suitable **statistical procedures** where appropriate. Examination and **testing of samples shall assure** that the drug product and in-process material **conform** to specifications."

Thus, these articles do not address:

a. Taking **representative** samples
b. Sampling and testing **phases** before the final blend phase
c. Assessing the "adequacy of mixing" for **ingredients other than the active ingredients**
d. Assessing **dissolution** time or rate (depending on which is required of the drug product)
e. Using suitable statistical procedures to determine valid in-process specifications for the active ingredients and the other ingredients that may affect drug product characteristics.

Based on the preceding alone, the articles propose inspection (sampling and testing) plans that are neither scientifically sound (as required by 21 CFR 211.160) nor CGMP-compliant since the sampling plans proposed do not:

a. Take suitable batch-representative samples,
b. Address all of phases in the production of a tablet drug product, or
c. Deal with all of the batch characteristics that the regulations require the firm to address.

Overall, the articles are pseudo-scientific exercises apparently aimed at justifying practices that the industry seems to be using with little or no regard to the clear CGMP ***minimums*** set forth in 21 CFR 211.

Paul G. King, Ph.D.
Facility Automation Management Engineering (FAME) Systems
Lake Hiawatha, NJ USA
Received October 3, 2003"

"**Acknowledgements:**
PDA thanks the members of the Blend Uniformity Task Force for their input in developing these comments.

Name	**Company**
James Bergum	Bristol-Myers Squibb Company
Jim Carron	Pharmaceutical Services Corporation
Bob Dana	Elkhorn Associates
Don Elinski	Eli Lilly and Company
Garnet Peck	Purdue University
Laura Foust	Eli Lilly and Company
Daniel H. Gold, Ph.D.	D. H. Gold and Associates, Inc.
David Long	Eli Lilly and Company
Russell E. Madsen	The Williamsburg Group, LLC
Jerome Planchard	Patheon
Richard Poska	Abbott Laboratories
George Robertson	PDA
Paul Vogel	Lachman Consultants
David Whiteman	Aventis Pharmaceuticals"

This reviewer trusts that each of the members of this "Blend Uniformity Task Force" will, *after carefully reading this review*, either:

a) Furnish this reviewer and the Agency with the *scientifically sound* and regulation conforming documents that support their positions **or**

b) *If the sound science and the regulations clearly support this reviewer's assertions*, publicly acknowledge the same as openly as they have espoused their present positions.

In the commenter's "Comment Grid" that follows, this reviewer has combined the first two columns in the submitted "grids" and discarded the header to provide more space for providing the reviewer's "Observation" and "Basis" statements that follow each of the commenter's entries in a format that is more easily read than that in the commenter's format.

PDA Comments (Labeled: 2-24-2004)

C-No. & Descriptor	Comment/Recommendation for Revision / **Observation**	Comments regarding test / **Basis**
#: 1 General Comment	The guidance avoids the term 'validation', using less descriptive titles like "verification of manufacturing criteria". We recommend including the term 'validation' and 'development' to clarify the purpose of various sections. First, the word "validation" appears eight (8) times in the body of the Draft so it is less than accurate for the commenter to assert that this draft "guidance avoids the term 'validation'." Based on the commenter's recommendation, it would seem that the commenter's real concern is that the titles do not use the terms "development" and "validation" when, ❖ In light of the recent revisions to FDA **CPG 7132c** in **Sec. 490.100**, "Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08)," official as of 12 March 2004, this commenter should have realized why the Agency avoided the use of the term "validation" in the titles of the sections in this drug product[1] guidance. ❖ Further, because this guidance applies generally, it is inappropriate to use the word "development" in the section titles because that word carries with it the connotation of an activity limited to new products when the draft guidance provided is clearly intended to be guidance applicable to all products. [1] **21 CFR 210.3(b)(4)**, "Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo."	The PQRI proposal clearly defines activities that are performed during development (pre-validation) and validation. The reluctance to use the term validation creates a disconnect with the PQRI proposal and makes the draft guidance more difficult to interpret. When addressing validation, the cited Agency CPG states (emphases added): "**Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110)**, and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. *A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. The* ***proof of validation is obtained*** *through rational experimental design and the evaluation of data*, preferably **beginning *from* the process development phase** and **continuing *through* the commercial production phase.**" Based on the preceding, ALL such "drug product" batches are "validation" batches as per **21 CFR 211.110(a)**'s "control procedures shall be established to monitor the output and **to validate** the performance of those manufacturing processes that …" for each batch and its use to differentiate between phase would, in light of this policy and the cited regulations, therefore be futile. The basis for not including, the word "development" in the section titles is explicitly addressed in this reviewer's observations. Moreover, under **21 U.S.C. 321g(1)**, *that defines a drug*, all "development" batches that are administered to humans or animals are drug product batches upon which firms must use control procedures "to monitor and validate …" **21 CFR 211.110**. Thus, the PQRI's understanding of CGMP is, at best, flawed.

C-No. & Descriptor	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
# 2 General Question	If, through development, we know that reliable blend sampling is unattainable (up to 10x) due to thief error and we have data to prove this, do we still need to pull blend samples during validation or can we skip sampling from the blend in validation and use Stage 2 dosage unit testing to demonstrate uniformity of the blend? This reviewer finds the commenter's proposition here represents a clear example of scientific psychosis to all who understand the fundamentals of material inspection as applied to complex blends of solid powders. In general, *when you have sampling problems*, at any level, you should: • First, identify the primary causes for the problem (component specification control issues, mechanical instability of the blend, sampling tool design, sample amount, and/or sampling technique). • Second, minimize or eliminate the cause or causes of the problem (improve the controls on the components, uniformity and/or mechanical stability of the formulation, sampling tool design, and sampling amount, and use the minimally invasive sampling techniques) until these sampling problems are minimized or eliminated. • Third, *after the sources of the "sampling problem(s)" have been identified and corrected*, perform inspection (sampling and testing) on sufficient blends to verify that there is no significant residual sampling bias. • Fourth, finalize the controls and procedures used in Specifications, SOPs and Work Instructions as appropriate. • Fifth, implement the proven procedures in all further studies. When the batch blend's volume reaches the size that precludes the taking of a *batch-representative* set of unbiased "mixer" samples of an amount sufficient for all replicates for all critical variable factors that require an independent sample work up, migrate your blend sampling point to the IBCs into which the blend is transferred after blending. [**Note:** In general, *for near-full-scale blends*, the sample amounts required for an unbiased sampling from each sample location are on the order of 10's of grams even though the unit-dose sample sizes for the testing are on the order of 50 milligrams to 1000 milligrams.] Efforts to get vendor to again provide free-flowing grade that met firm's particle-size specifications and the proposed flow specifications (derived from study on the retains from previously acceptable API lots) were not successful. Firm ceased manufacture of this drug product because root cause of the problem (API flow) could not be resolved (API source uncooperative).	Continuing to use a flawed test would not add meaningful data to the Validation exercise. This does not remove the obligation of the firm to use good science to continue the search for more robust sampling methodology. While this reviewer agrees that it is folly to continue "to use a flawed test," this reviewer knows that, as the commenter states, "the obligation of the firm to use good science" is an absolute obligation that must be met. However, the commenter's proposal accepts as "gospel" that the root cause for the "blend sampling" problems is in the tool or technique used when, *based on this reviewer's experience*, the "root causes" are most often in the formulation or formulation processing operations or, almost as often, sub-standard or missing controls on one or more components. Thus, though it is all too easy to blame the sampling tool or technique rather than a sub-standard formulation or sub-standard component controls, as the commenter's remarks clearly indicate, this reviewer counsels that the root cause(s) for the "blend sampling" problem found must be identified and appropriate root-cause-corrective actions taken. **Two illustrative examples come to mind:** **1. Blending-Related Non-Uniformity** *In development of a direct blending process, the firm put a blue dye in "10 mg" strength of the formulation and a yellow dye in the "20 mg" strength to differentiate them from each other even though the weights of the tablets were proportional.* *Using the lab formulation procedure developed without the dyes), the studies found the "0.1 % yellow dye" final blend was uniform but the "0.09 % blue dye " one was not.* *A microscopic examination on small-scale blends found that, relative to the dye-free blend, while the yellow dye used promoted blend uniformity, the blue dye caused* active agglomeration that prevented uniformity from being achieved. The problem was "solved" by changing the dye used to a different one that did not trigger agglomeration of the active. **2. Component-Related Non-Uniformity** Approved process that had "no history" of significant problems (based on CU testing) "suddenly" experienced multiple uniformity problems found in released batches by FDA. Investigation found root cause was a fundamental change in the flow properties (for which the firm had no specification) of the active pharmaceutical ingredient. (←Continued in adjacent column)

C-No. & Descriptor	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
# 3 General Comment	There is a key piece missing in the guidance and that is a review of the Method development summary report and the method validation package. While this reviewer recognizes the requirements for the firms' quality control unit (QCU) to review and approve the methods used for testing (**21 CFR 211.22**), this requirement is not a "key missing piece in the guidance." The key missing pieces in this Draft are the failure to provide for or require: **a.** The development and use of *scientifically sound* and *appropriate representative-sample sampling plans* that take unbiased samples of a suitable size (amount or number) for the evaluation of all of the critical variable factors in a given drug product formulation. **b.** The use of recognized consensus standards for setting *scientifically sound* and *appropriate sample test numbers* and *batch acceptance criteria* for the any discrete units phase in the manufacture of the drug product. **c.** *Scientifically sound specifications* that are *appropriate* for the *samples* and the *batch* and that, if met, ensure that *each accepted batch* has a high degree of assurance that all the dosage units will, if tested, pass.	These two tools are the key to discovering a root cause of an analytical error. This is especially important when an unidentified analytical error continues to occur. This evaluation should occur concurrent with a lab investigation. This review should be performed before any retesting has occurred. The documents if well defined will provide guidance on where the method has critical steps that may not be defined. In addition a well-written controlled document will have described why critical changes were made to the methodology. In the cases of compendia1methodology it is always good to look at the method validation of the firms own product. This will demonstrate where the application of the compendia1 method on the firms product may not be as rugged or robust. Factually, QCU review is a single tool. Moreover, this activity should precede any "for purpose" use of any method. In addition, *each time a method is used*, the CGMP regulations require, "… The suitability of all testing methods used shall be verified under actual conditions of use." (**21 CFR 211.194(a)(2)**) If these activities are conducted as required by CGMP, there should be no need to do as this commenter suggests. Thus, the commenter's suggestions should be placed in a guidance that addresses methods and the ongoing "each batch" validation journey that applies to methods rather than in this guidance.

C-No. & Descriptor	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
# 4 **Line 58**	The following lines are suggested for inclusion in the Scope: "After Readily Passing all validation batches, products that are allowed to meet USP requirements using content uniformity by weight variation are exempted from future routine blend testing requirements." This reviewer cannot agree with the commenter's proposal because it ignores the clear applicable requirements of the CGMP regulations that bear on in-process materials and in-process dosage units for each batch of all drug products. Moreover, this reviewer is at a loss to see how the **USP**'s discrete dosage-unit requirements can be directly applied to the non-discrete final-blend samples. In addition, this reviewer notes that this draft guidance deliberately and improperly ignores: • **USP**'s expectations for the range for the content values found not more than (NMT) 1 in 30 outside of 85 % to 115 % of the **USP** target for "tablets" and, for capsules, NMT 1 or 2 in 30 outside of 85 % to 115 % of the **USP** target for "capsules." • Explicit ***General Notices***' requirement that the mean found must be "100 %" of the label claim or **USP** Assay's mid-range value, and • The explicit **USP** "blend (from which the dosage units were formed) is uniform" assumption contained in the **USP's** *Uniformity of Dosage Unit* test procedures.	The PQRI report to the FDA recommended the exclusion from the requirements of the guideline those products where the determination of dosage0-form uniformity by weight variation is allowed. The former BU draft guidance for ANDA products also excluded these products. Again, the PQRI shows it lack of understanding and deliberate disregard for the applicable CGMP regulations governing in-process materials and in-process drug products. By law, the **USP**'s procedures ONLY apply to released drug product batches in commerce. Moreover, the comment does not require *batch-representative samples* nor, *in the case of the dosage units*, does it test sufficient dosage units to meet the clear requirement minimums of the applicable CGMP regulations, nor, for that matter, the recognized number minimums set forth in the applicable consensus standards (*which are designed to provide a 95 % level of confidence that the sample results are predictive of the active content properties of the batch*) for the "process variability unknown—standard deviation" case which clearly applies to dosage units produced from components for which the manufacturer does not even identify, *much less rigorously control*, the critical physical properties for said components and materials used to manufacture said dosage units. [**Note:** In general, the maximum **USP** number, 30 units, *if taken from a batch-representative sample*, furnishes *batch uniformity estimates that* can only *predict* the *batch's active uniformity* at a confidence level that is **less than 20 %**.]

C-No. & Descriptor	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
#5 Line 60	Change line 60 to read: "Stratified Sampling of dosage units is the process of sampling at predefined intervals and collection… ." While this reviewer agrees that the commenter's suggested word order is more appropriate than that in the Draft, this reviewer cannot support the use of "***stratified sampling***" as defined by this guidance because: **a.** It does not require that the sampling points to be *representative* of the batch; **b.** Since the Draft proposes ***dynamic sampling*** (sampling while the dosage units are being formed), but does not require, *as it should*, that the samples at each sampling point must be ***representative*** *of* the *local variability at* the point in *time* where *each sample* is taken; **and** **c.** Does not require that the *number* of dosage units sampled should be more than the number required for ***batch-representative*** evaluations for all of the ***critical variable factors*** that **may** adversely affect the uniformity of the in-process materials and the in-process drug product. [**Note:** The drug product batch is an in-process drug product batch until the firm's QCU releases it for distribution.] Moreover, this reviewer suggests that, contrary to the commenter's statement, the sampling alluded to takes place at "predefined (time) points" – not at "predefined intervals." This reviewer must therefore recommend that this draft guidance be revised until it conforms to: ➢ The fundamentals of sound inspection science as they apply to the dynamic sampling of units from batches of units **and** ➢ The clear CGMP requirement **minimums** for the in-process materials and the drug product.	The term "stratified sampling" in italics implies a definition. The appropriate technical definition for stratified sampling is not limited to dosage units ; thus, the order of the words should be changed to comply with the PQRI proposal and definition. As per **21 CFR 211.160(b)(2)**, all in-process samples must be a ***representative sample*** of the batch of material as the term "***Representative sample***" is defined in **21 CFR 210.3(b)(21)** (emphases added), "***Representative sample*** *means* a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the ***sample*** *accurately portrays the material being sampled*," and, *as defined in this draft*, "**Stratified sampling**" does not meet the requirement **minimums** established in the CGMP regulations for drugs. For *dynamic sampling*, sound inspection science requires that each sampling point sampled must take a sample that is ***representative*** *of* the *local variability at the time of sampling* and this Draft does not even address this issue. The precepts of sound inspection science also require that the sample sampled should be of sufficient size (number) for all evaluations (of *all* the variable factors that should be evaluated, not just active content) that may be required since, for ***dynamic sampling***, it is not possible to go back (unless you have a time machine) and take additional samples at a sampling point. Since sound analytical science dictates that the sample sampled should be at least large enough for a test, a retest and a reserve (as Judge Wolin found in *USA v. Barr)*, the minimum number that must be sampled must be *at least* three (*3*) *times* the *number* required for ***all*** of the *variable factors* that must be assessed. In the CGMP regulations, "**Sec. 210.1** Status of current good manufacturing practice regulations" and "**Sec. 211.1** Scope" both clearly establish that the requirements in the CGMP regulations are **minimums** – a firm cannot do less and comply.

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# 6 Lines 95-97	Remove sentence, "Formulations with extremely low dose and/or high potency may call for more rigorous sampling…units. This reviewer does not concur with the commenter's suggestion because the sentence states a factual reality. Therefore, this reviewer strongly recommends that this sentence be retained in the final guidance.	Sentence is ambiguous in that it calls for more rigorous sampling, but gives no guidance or reference to how to accomplish these ends. The sentence is not ambiguous; it clearly calls for more inspection when the level of active is extremely low. That it does not prescribe what should be done is appropriate because the proper course of action depends upon: **a)** the level of the active **and b)** its uniformity in the final blend.
# 7 Line 99	Remove sentence When using the methods. . maybe observed. This reviewer does not agree with the commenter here.	Observation of trends is obvious. The sentence adds nothing to the dialogue. *Based on the Industry's repeated failure to recognize and/or respond to trends in their manufacturing and other operations*, there is nothing "obvious" about suggesting that one needs to look for trends.
# 8 Line 100	Remove the words "these types of". This reviewer agrees with the commenter's suggestion here	For Clarity
#9 Line 108	For clarity: Change the section title so that it clarifies that these exercises are Development (pre-validation) procedures. One possibility: "IV. Evaluating Powder Mix and In-Process Stratified Sampling During Process Development" Though this reviewer cannot agree with the commenter's suggested alternative, this reviewer does agree that this title should be revised. Based on the commenter's input, this reviewer suggest the title be changed to: "**IV. Establishing Sound In-process Active Uniformity Specifications For the Various In-Process Non-discrete Materials, Including the Final** ~~Evaluating~~ Powder Mix, and the **Discrete In-Process Dosage Units Produced** ~~Stratified Sampling During Process Development~~ **From the Non-Discrete Final Blends**"	It is not clear (to all readers) that this is a separate procedure from that proposed in Section V. A title and purpose statement will help clarify the reason for the difference in sampling scheme and lack of acceptance criteria. Properly, this section should address the issue of setting *scientifically sound* and *appropriate specifications* for each non-discrete in-process material and the in-process drug-product units produced by a given drug product process and not, as the commenter's suggested title indicates, activities that are exclusively associated with process development. Moreover, the title suggested by the reviewer clearly indicates that this section of the Draft addresses the setting of specifications for each active-containing in-process material (not just the "final blend" from which the dosage units are formed) and the discrete in-process formed dosage units for active uniformity – one of several critical variable factors that must be appropriately controlled and evaluated in each in-process batch of drug product. Titled as this reviewer suggests, the purpose of this section should be clear to all.

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# 10 Line 115	Change line 115 to read: "through assessment of data from development batches. This reviewer does not agree with the commenter's suggestion and, *in keeping with the title this reviewer has proposed*, suggests that the text in Lines 111 – 119 be revised to read: "If you plan to follow the procedures described in this guidance document, we recommend that you first complete the ~~process~~ specification development procedures described in this section before using the methods described in sections V, VI, VII. The subsections below describe how to assess the adequacy of the various discrete in-process materials produced, including the final powder mix, the uniformity of the active content of the discrete in-process and finished dosage units through ~~correlation~~ comparison and assessment of data from development, validation and manufacturing batches. The purpose of these studies is to aid the manufacturer in establishing *scientifically sound* specifications for the uniformity of the active that appropriate for establishing the acceptance criteria for each non-discrete, in-process material as well as for the discrete formed and finished dosage units in each batch. These ~~procedures~~ studies can reveal deficiencies in the blending operation that may not have been previously detected. We recommend that manufacturers correct all deficiencies in ~~the blending operation~~ their non-discrete material production steps before implementing the routine manufacturing control methods described in this guidance."	This section (Set IV) is done prior to validation (per line 112), so the reference to validation and manufacturing in line 115 is confusing. Since the confusion is introduced in Line 112, when the phrase "process development" is used when the phrase "specification development" is clearly the more appropriate, this reviewer has suggested correcting the Line 112. In keeping with the revised title suggested, this reviewer suggests modifying the rest of the paragraph in the manner suggested.
# 11 Line 123	Add a 'purpose statement' to this line. For example: "As a part of development, we recommend that you assess critical events in the blend process and determine appropriate sampling techniques for demonstrating a validated blend process. As a part of this evaluation, we recommend the following procedures." This reviewer does not agree with the commenter's suggestion because it falsely asserts that the reason for the added wording is "for demonstrating a validated blend process," something that, because validation is, *as the Agency clearly recognizes and the in-process CGMP regulations specify*, an ongoing "each batch" journey and not a destination. IF the guidance is restricted to the assessment of active uniformity, this reviewer offers the following: "As part of specification development, we recommend that you establish that each of your: **a)** Discrete-material sampling plans produces unbiased samples sufficient in amount for all evaluations and **b)** Test procedures appropriately samples and evaluates duplicate unbiased unit-dose, or smaller, sample aliquots from each sample so that you can thereby prove the validity of the results you obtain." As a part of these procedures, we recommend that you use the following procedures to assess the uniformity of each active in each non-discrete active-containing material produced by the drug-product manufacturing process you are evaluating."	Clarify, to help others understand the importance of the section. **21 CFR 211.110(a) –** the clear "each batch" "to monitor … and to validate …" requirements contained therein clearly establish that validation is a journey and that no process that is being used can properly be considered to be validated – at best such can be considered "valid" or "supporting the validity of the overall process." **See also**, the discussion on validation contained in Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08) of the FDA's Compliance Policy Guide 7132c effective 12 March 2004.

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# 12 Lines 137 & 140	We suggest changing the word "Significant" to "High" in both lines. This reviewer rejects this obviously wrongheaded suggestion. Since the texts in question are discussing statistical measures (*within-location variance* and *between-location variance*, respectively), the word "Significant" is obviously the appropriate word to use.	Because the term "significant" may imply "statistical significance." The change would avoid confusion and comply with PQRI terminology. When the texts are clearly discussing a statistical measurement (variance) the change suggested is inappropriate whether, or not, it meshes with the PQRI terminology. For *variance*, tests of "statistical significance" are exactly what should be used.
# 13 Line 146	Add a 'purpose statement' to this line. For example: "Prior to validation, we recommend that you assess the in-process dosage unit data to identify locations throughout the compression/filling operation that have a higher risk of producing failing finished product uniformity of content results and to identify the stratified sampling that may be used to verify powder mix uniformity. We…" Though this reviewer has no objection to adding a "purpose" statement, This reviewer finds the commenter's suggested text is both at odds with the principles of validation and unrealistic. Until the flawed guidance offered is corrected in a manner that fully conforms to the applicable requirement minimums of the CGMP regulations this reviewer cannot recommend appropriate wording. However, this reviewer notes the following problem areas that should be addressed by the Agency: 1. The multi-level analysis of the final blend material in the IBCs used to charge the feed to the dosage forming equipment 2. Sampling a *representative* number of units from each dosage-forming station at each sampling point. 3. Evaluation of a *representative* subset from each sample sampled from the in-process dosage units. 4. Linking the uniformity of the material in each IBC to the uniformity of the dosage units formed from it, 5. Restricting the guidance to the uniformity of the active or actives present.	Clarify, to help others understand the importance of the section. *Since most recognize that validation begins in development and labels that phase as the Design/Development Qualification phase (DQ)*, the actions suggested here fall within the validation envelope. *Unless the guidance provides some mechanism (like the one suggested) to link the results from the some part of the final blend to the results for the dosage units produced therefrom*, there is no way to effect the identifications suggested. *Unless the guidance is restricted to the uniformity of the active or actives*, measuring active level does not address or ensure overall uniformity. *Because dynamic sampling is the sampling used*, the failure to require the taking of at least one unit from each dosage-unit-forming station at each sampling point fails to ensure that the samples are *representative* of the *batch*. *Under the present scenario*, all that can be compared is an uncertain final blend's active uniformity based on biased samples to a non-representative-sample-based even less certain estimate of the active uniformity in the formed dosage units sampled. *Under the Draft's scenario*, the weight-corrected active content values computed from the biased dosage results are biased estimates of the variance of the blend plus variance of the transfer operations, the variance introduced by the dosage-unit-forming process, and the lumped "error" variance.
# 14 Line 149	Remove the words, "and location". This reviewer does not, *per se*, object to the commenter's suggestion here unless the "and location" was meant to guide the reader to taking samples from all dosage forming stations at each sampling point. However, this reviewer suggests that "intervals" be replaced with "sampling points."	The term location in reference to compression or filling is confusing. Interval is the standard Industry descriptor. Properly, "sampling interval" is the appropriate term for sampling that collects a sample across some interval and "sampling point" or "sampling time point" is the appropriate term for sampling that occurs at some point in time.

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# 15 Lines 160-161	Change lines 160-161 to read "Prepare a summary of the data (and analysis), identifying the significant events in the manufacturing process that may impact blending and from this, identify the stratified sampling that may be used to verify powder mix uniformity. We…" This reviewer does <u>not</u> support the commenter's suggested wording for the cited text for the same reasons as he has presented previously. Provided the draft is restricted to <u>only</u> assessing the uniformity of the active or actives and the text is modified to require the in-process dosage units evaluated to be <u>not</u> less than 200 batch-representative units (for "NORMAL" inspection) and the results composed of the values found for an equal number, chosen at random, from each routine sampling point and any additional sampling points, this reviewer suggests the following alternative: "• Prepare a summary of the data including the specific content values (content values corrected to the target unit or unit-fill weight) for each tablet tested and the corresponding statistical estimates derived therefrom, minimally at the 95-% confidence level, and compare those statistical estimates to the corresponding statistical estimates for the active level in the final blends." 8. Compare the results from each IBC to the weight-corrected results from the tablets linked to the IBC. 9. Compare the statistical estimates of the batch result limits for the blend to those from the in-process dosage units. 10. Enter all results into an appropriately constructed table. 11. Use the appropriate statistical analysis procedures and a confidence level of not less than 95 % to analyze all of the data and generate appropriate findings as to the predicted active uniformity of the blend and the in-process dosage units as well as the relationship, if any between IBC results and the related in-process dosage units. 12. Report all data and findings. [**Note:** If the active's variance for the in-process dosage units is significantly larger than that for the blend, investigate and, *when the cause has been found*, take corrective action.]	To clarify purpose and prevent some confusion over the use of the term 'correlate'. Comparing biased estimates of the blend's active uniformity from a few singlicate (ca. 20) non-representative blend results with no local estimate of result reproducibility to the in-process dosage-units' active uniformity from a few (ca. 140) non-representative dosage-units' results that are, at best, weakly linkable as in the Draft's scenario is a less than scientific procedure. If the guidance is restricted to active uniformity and, in development, the guidance should direct that you should: 1. Sample unbiased samples from multiple levels in each of the IBCs from the final blend and perform duplicate aliquot tests (with at least two measurements on of the active in each aliquot) on each sample from each IBC in a manner that links the results to the location in the IBC location from which it came. 2. At not less than 20 sampling points across the production of formed dosage units, take not less than four (4) dosage units for each dosage-unit-forming station *at each sampling point, "routine"* ("start," "n points," and "end") and "*significant event"* (e.g., restart, hopper rundown), and collect each in a separate, appropriately labeled container, 3. At each sampling point note the IBC container number and approximate level of the blend that is being formed while all samples are being collected. 4. From each "routine sample" sampling point container, take not less than ten (10) dosage units chosen at random from that sampling point and label the test-sample container with its sampling point ID. 5. At each "significant event" sampling point container, take not less than ten (10) dosage units chosen at random from that sampling point and label the test-sample container with its sampling point ID 6. Weigh and analyze all samples in a manner that provides at least two valid measurements for each dosage unit and preserve all result, ID and weight links. 7. Compute the weight corrected active level for all active level results. (← Continues in the adjacent column)

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#16 Lines 163 - 164	Change "data described above" to "uniformity" While this reviewer does not oppose the commenter's suggested change, the entire sentence should be changed to read: "For each active, compare the statistical batch estimates of its powder mix uniformity to the statistical batch estimates of its in-process weight-corrected dosage-unit uniformity."	Compare powder mix uniformity to dosage unit uniformity (clarity) *For scientific accuracy*, the text should make it clear that: **a)** only one aspect (the uniformity of the active or actives) of the *overall batch uniformity* (active, active availability, etc.) is being compared and not, as the text implies, the overall uniformity **and b)** the comparisons should be based on sound statistical estimates of the *batch*'s parameters and not directly on the values calculated for the samples tested.
# 17 Lines 169-170	Examples of state of the art should be given or one could generally use the P.A.T., Process analytical Technology as a descriptor example. This reviewer does not agree with the commenter's suggestion, but would recommend changing the sentence in Lines 168—170 to read: "Sampling problems can, in some cases, also be eliminated by the use of alternate state-of-the-art analytical systems that have been proven to provide valid in situ real-time sampling and analysis."	Clarity The text here should be more general than the limited systems described by the proponents of. P.A.T.
#18 Line 172	Change section title to "Establish the relationship between stratified in-process samples and the finished product" This reviewer does not support the commenter's suggested change. Provided the sampling and the sample evaluation plans are changed to specify that all must be *representative* and the guidance is restricted to the active or actives, this reviewer would recommend changing the cited title to: "**Comparison Of the Uniformity Of the Active(s) In Dynamically Sampled In-Process Dosage Units To the Uniformity Of the Active(s) In the Finished Product**"	Clarity, also removes the term 'correlate' which has statistical connotations. Since the Draft, as written, does not even sample, or evaluate sufficient (in number) *batch-representative samples* to establish, with a high degree of confidence (95 % or higher), unbiased estimates of the uniformity of the active (or actives) in either the freshly formed in-process dosage units or final in-process drug-product dosage units, the current Draft only validly permits you to crudely "compare" the two (2) estimates of the uniformity of the active or actives. Furthermore, the current guidance is clearly at odds with the applicable CGMP regulations and must be corrected until it fully conforms to the requirement ***minimums*** established in said CGMP regulations. Finally, until a body ($\geq$ 15) of production-scale batches has been accumulated over a significant time period ($\geq$ 1 years), all that you should do is ***compare*** the uniformities observed for the two dosage-form phases – proving the overall relationship requires a significant body of evidence.

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# 19 Lines 172-185	Reformat for clarity: Move this section under the topic of Section VI, with the additional option that if this verification has previously been completed in development, that it is not necessary to repeat the evaluation. This reviewer cannot agree with the commenter's suggestion here as it flies in the face of both common sense and sound science. If you cannot find in development that the uniformity of the active content in the freshly formed dosage units is comparable to the uniformity of the active in the finished dosage units in all the development-related batches, either the process in question falls outside the scope of this guidance (e.g., more of the active is added in one or more coating steps) or, *if the drug product definitely falls within the scope of this guidance for assessing the uniformity of the active*, your product development activities have, to date, been inadequate. However, the guidance furnished in the Draft clearly conflicts with many of the requirements set forth in **21 CFR 211**. Therefore, this reviewer again strongly suggests that this section of the guidance be revised until it conforms to all of the applicable requirement minimums set forth in the CGMP regulations.	Most companies will use the extended testing during validation to compare in-process to finished product, in order to obtain better estimate. During development, it may not be practical to obtain a sufficient amount of data to demonstrate equivalency or 'correlation' between final and in-process product. It should be obvious that a drug-product falling within the true scope of this guidance (*assessing the uniformity of the active or actives* in the in-process materials and the drug product [a single-layer, single fill tablet or capsule made from a single uniform final blend]) must have an active uniformity in the freshly formed dosage units that is comparable to the active uniformity on the finished dosage units tested for release for distribution (for each active) or the process development needs to be continued or restarted. However, the guidance in this section does need significant revision to ensure that sufficient *batch-representative* drug-product samples are appropriately evaluated against *scientifically sound* and *appropriate specifications* which ensure that all of the untested units in the batch will, after the batch is released, meet the **USP**'s "in commerce" requirements. If the uniformity of the active is the only aspect of the assessment of the uniformity of the drug product, the minimum number of drug-product samples that must be tested is on the order of 200 (the minimum number that should be tested is on the order 300 to 900 representative units depending upon the level of confidence required for setting process' projected limits and initial specifications). The *scientifically sound* and *appropriate acceptance criteria* should include those established for the batch in the recognized consensus standards for the inspection of variable factor for the percent nonconforming published by ANSI and ISO. This is the case for drug products because, *for release*, the drug product dosage units must meet the requirements set forth in **21 CFR 211.165(d)**.

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# 20 Line 174	Add a purpose statement to this line: "In order to use in-process samples to fulfill the compendial uniformity of dosage unit requirement for finished products, we recommend the following steps:" This reviewer cannot agree with this commenter's statement because it is not factually true. The clear applicable CGMP requirement ***minimums***, and not the **USP**'s post-release ones, are the legal binding requirements that, *under law*, each manufacturer must establish and use to assure that *each batch* (of drug product the manufacturer accepts for release into commence) is not adulterated as that term is defined in **21 U.S.C. 351(a)(2)(B)**.	It is currently unclear why this section is important. The commenter's'' remarks do little to make it clear "why this section is important." Factually, there is **no** "compendial uniformity of dosage units requirement for finished products" ***prior to*** the ***release of*** the ***batch*** nor, *for that matter*, are the **USP**'s requirements applicable to other than the *post-release* "in commerce" *article*, as said *article* is defined by the **USP**.
# 21 Line 186	We suggest adding another bullet point: "If the in-process samples cannot be used to assure the uniformity of dosage units, then the compendial test on the final product will need to be continued in addition to in-process stratified testing for blend uniformity." This reviewer supports adding another bullet point. However, as the reviewer's remarks in the previous row clearly support, the text proposed is clearly at odds with CGMP and should not be used as the basis for that bullet point. Instead, this reviewer proposes adding the following CGMP-compliant bullet point: "If the active content results for the in-process samples tested using the appropriate 'process variability unknown,' 'normal' inspection plan in ISO 3951 or ANSI Z1.9 indicates that the batch fails to be sufficiently uniform, then, unless the sample results are all inside of the **USP**'s post-release requirements of '75 % to 125 % of target,' the batch under test should be rejected and an investigation that has the goal of finding the root cause(s) and implementing the requisite root-cause-corrective actions should be started. In cases where the batch acceptance quality level is not met but all values are inside of the **USP**'s any-unit limits, then, after initiating a root-cause investigation, an appropriate augmenting set of batch-representative sample units (typically the same number as required for the full initial test) may be tested and the results evaluated using a distribution-free approach to assess the batch's acceptability provided the firm's inspection plan are hierarchical in nature and explicitly provide for this option. Otherwise, such developmental batches must be rejected."	The bullet provides guidance and flexibility if a relationship cannot be established at that time. First, all of the reviewer's applicable prior remarks concerning what is required for acceptable uniformity for the active or actives in the in-process dosage units (whether they are freshly formed or finished dosage units) are incorporated by reference. Nowhere in the CGMP regulations governing all aspects of the drug product's production do the regulations permit the in-process evaluation of non-representative materials or drug product units. . The **USP**'s sample and test plans only apply to post-release materials in commerce – they do not apply to in-process materials and in-process drug product. As the **USP** clearly states, the **USP**'s sampling plans are not statistical sampling plans (statistical sampling plans are a prerequisite for a representative sample) and the USP's specification limits can only be directly applied to the **USP** "article" after the batch is released. *Based on the preceding*, under CGMP you cannot be complying with the applicable CGMP regulation ***minimums*** if you are directly using the **USP**'s post-release inspection plan and acceptance criteria for releasing batches of in-process dosage units and/or the drug product in the development phase. [**Note:** The only possible exception to the preceding would require the entire batch to consist of 500 dosage units or less – but even here the acceptance criteria would have to be appropriately inside of any limits range or inside of any single limit specification because you are only testing a small percentage (6 % for a 500 dosage-unit batch) of the batch.]

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# 22 **Line 188**	Validation is misspelled. This reviewer agrees.	Spelling error.
# 23 **Line 195**	Remove the word "independently" This reviewer agrees with the commenter here.	Although data are collected and analyzed separately, the overall assessment must include evaluating both dosage unit and blend data as a whole. The addition of this word in this sentence does not add value and may confuse.
# 24 **Line 198**	Insert the words "if practical" after the word blender. Alternatively, the words "in the blender" could be dropped. While this reviewer does not object to this wording change, this reviewer knows that the entire approach should be revised. Considering the fundamentals of sound inspection science and the requirements of the CGMP regulations that clearly require the inspection of each batch of each distinct in-process material produced during the production of the drug product, this reviewer proposes the following alternative for the steps in the draft *provided that draft is restricted to the assessment of the uniformity of the active(s) in each batch of drug product*: **1.** *For each distinct in-process non-discrete 'powder' product produced (e.g., mix, blend, fusion)*, select that minimum set of post-production locations that development has proven to be *representative* of the uniformity of the active or actives in the material being sampled. [**Note:** When sampling the materials as a whole from a *conformance batch*, that set should consist of not less than (NLT) 15 locations and, when sampling from a set of NLT 5 IBCs, that set should consist of NLT 1 sample from the top, middle, and bottom of each IBC. The sampling plan used must span the batch and, *for the material as a whole*, appropriately include at least one sample from a location that previous studies and information have proven to represent, on average, the "least uniform" material as well as one from the corresponding similarly proven to represent the "most uniform" material location.] **2.** *From each of the representative sample locations identified*, use a proven unbiased sampling and sample handling procedure to collect an amount of material that is adequate to provide an unbiased sample that is at least three times the amount needed for the evaluation of all of the critical variable factors in the material, including the active or actives. Place each unbiased *location-representative sample* into a properly labeled container that is sized so that the sample fills the container, close the sample container, and place it upright in a suitable transport carrier. (Continued on next page)	Some blender installations due to size of the blender or room considerations do not lend themselves to safe or practical sampling in the blender. In such cases sampling from drums after discharge may be justified as long as location sequence is maintained. Factually, sampling from the IBC's should be the point at which most production-scale blends are sampled. When this is the sampling point, the blend distribution includes the non-homogeneities, *if any*, introduced by the transfer of a blend from the mixer into the IBCs. However, this reviewer knows of no certain way to establish, *much less maintain*, "location sequence" between the material at a given location in the blender and the exact same material in the IBCs.

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# 24 **Line 198** (Continued)	(Continued) **3.** *After collecting all of the required location-representative samples required to generate a batch-representative sample (as required by **21 CFR 211.160(b)(2)**)*, transport said *batch-representative sample* to where it will be evaluated. **4.** *At the evaluation location*, carefully remove two (2) unbiased approximately *unit-dose aliquots* from each sample sampled and prepare them for analysis. Retain the samples sampled for use in the evaluation of other critical variable factors. When the entire set has been prepared, randomize the evaluation order of the prepared samples and along with the appropriate standard preparations evaluate the samples in a manner that the results consist of two or more measurements (or a valid instrument-averaged equivalent) of each sample-aliquot preparation. **5.** Appropriately analyze the valid results obtained against the *scientifically sound sample specifications* established during development as well as the appropriate *batch acceptance criteria* derived from the sample results found. **6.** Have your QCU determine whether or not the samples tested meet the specifications established and predict that the batch has an acceptable level of uniformity for all actives present in the material being evaluated. **7.** When the material is acceptable, the QCU should accept the final blend for release for use in the next production step pending the completion of all other variable assessments; if the QCU cannot accept it for release, quarantine it appropriately and initiate an investigation to determine the root cause(s) for the failure and the corrective action, if any, that has a high degree of certainty of bringing the material up to expectation, and, after QCU approval, proceed as your QCU directs. **8.** Incorporate all findings into the Process Performance Evaluation that should be an integral part of the initial conformance assessment for the drug product. **9.** In general, you must establish the validity of all your *sample specifications* and derived *batch acceptance criteria* for active uniformity, and, except for the last non-discrete material, no general prescriptive guidance has been suggested for these	
# 25 **Footnote 14** **Page 6**	Replace tablet with "dosage unit". This reviewer agrees with the commenter here.	Guidance covers both tablets and capsules.

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# 26 Lines 205-210	Line 205 (#2) should contain: 2. Collect at least 3 replicate samples from each location. Line 208-209 should be changed from a 'bullet' to a '#3', adding the deleted sentence from #2 to the end: 3. Assay one sample per location (.....blender). Samples should meet the following criteria: Since this reviewer has established that the sampling plans, testing procedures, and specifications established in the draft guidance are neither CGMP complaint nor *scientifically sound* and *appropriate*, the changes proposed by this commenter should not be made. If the Agency intends to provide a generalized "all critical variable factors" guidance, then none of what is suggested has merit. If, on the other hand, the Agency limits the guidance to ONLY the uniformity of the active and reworks the text to clearly reflect that change, then some of what the commenter has said could, with the changes suggested, be incorporated into such an "active uniformity" guidance.	Instructions about how many to assay should be before, not part of, acceptance criteria provided on lines 211-213. The commenter's rationale is the only thing that this reviewer almost agrees with – the word "test" or "evaluate" is more appropriate than the word "assay" However, the sampling plan and test plan are respectively scientifically deficient and analytically absurd. The "final blend" sampling plan violates CGMP by deliberately setting out to take a set of samples that is **not** *batch representative* as required by **21 CFR 211.160(b)(2)**. Second, *contrary to sound inspection science*, instead of collecting at each location a single sample of sufficient size for not less than three complete evaluations for each critical variable factor in the final blend (not just the active), instructs the reader to collect three "replicate" samples (as if that were possible) at each location. Third, *contrary to sound analytical practice*, only a single aliquot is analyzed from each sample precluding any estimate of the within-location variation at each location. Based on the preceding, the entire approach and criteria established are neither *scientifically sound* nor *appropriate*.

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# 27 Line 216 (revised)	The following revision of the revision suggested: If the samples do not meet these criteria, we recommend that you investigate the failure according to the flow chart in Attachment 1. Assay the remaining replicate blend samples. To aid in investigating the cause of failure, dosage from samples (seven form at least 20 locations) may be analyzed. These samples should have been obtained following the procedures described in Section VI, Verification of Manufacturing Criteria. If the cause of failure is not because of mixing, but is attributed to sampling error, or other problem(s) unrelated to the homogeneity of the blend, we recommend that you proceed with the evaluation of the dosage form data as described in Section VI. Because the CGMP regulations require *blend inspection* and *blend release* prior to the initiation of dosage formation and direct that *failing in-process materials must be quarantined* and withheld from use until an investigation can determine they are suitable for the step in which they are to be used, this reviewer cannot support the commenter here. In addition, the suggested course of action is at odds with the fundamental precepts of the "cost of quality" that counsel investigation and appropriate corrective action before you proceed with the manufacturing process. In addition, this reviewer cannot support the guidance proposed because, as published, it does not take a *batch-representative set* of *unbiased samples* of an amount in excess of three times the amount needed for the evaluation, in duplicate, of all of the critical variable factors in the final blend or evaluate unbiased duplicate aliquots from each sample for the level of active(s) in each sample sampled. Until this guidance's fundamentally flawed approach to blend sampling and blend-sample evaluation is corrected, this reviewer sees no value in commenting further about the Draft's present sampling plan or the equally flawed scheme associated with it. *Provided the inspection plan and decision schema are corrected in the manner suggested in this reviewer's previous remarks or a equally or more CGMP-compliant inspection-science conforming manner*, this reviewer suggests, as does the commenter, that finding of a failure should trigger an in-depth root-cause investigation designed to identify the root cause(s) of and the appropriate corrective actions for the failure observed. (Continued)	Attachment 1 needs to be slightly revised to conform to this change in wording. The box containing the text, "Assay at least seven dosage units per each location, weight correct each result" should be moved to be just under the box containing the text, "Assay 2nd and 3rd blend samples from each location" If you have truly identified and controlled all critical sources of variability, this reviewer, the Agency, and other scientists who understand the development of drug-product processes for tablets and capsules expect that failures of the valid active content blend results to meet *any* of the blend's ***scientifically sound*** and ***appropriate sample*** *specifications* and *batch acceptance criteria* should be rare. Sound inspection science for non-discrete materials dictates that each sample must be an unbiased sample that is larger than the amount required for a full test, retest and reserve for all the critical variable factors to be evaluated. In addition, for *batch-representative sampling*, the sample locations chosen must be proven, in development, to be sufficient to span the batch and include samples from all types of areas including the areas where development has established the "worst" and the "best" uniformity results for all critical variable factors have been consistently found in addition to areas where the blend consistently has been found to have similar uniformity with respect to all critical variable factors – not just to the active or actives in the formulation. To ensure that you can obtain valid estimates of the within-sample variability and to provide a check for possible analytical bias, this reviewer must recommend that each unbiased sample should have unbiased duplicate "unit dose" (or smaller" aliquots removed and evaluated. The upper limit on the evaluation amount in any material should be "unit dose" because that is the drug products' nominal unit of uniformity. However, when the tablet is scored and the dosing directions include the breaking the dosage unit into halves or thirds and taking half or one-third, you should seriously consider blend sampling at the "half unit dose" or "on-third unit dose" level. (Continued)

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# 27 Line 216 (revised) (Continued)	(Continued) However, *because the sample-evaluation plan should include adequate safeguards (in the reviewer's view, duplicate "unit dose" aliquot evaluations with duplicate measurements of each aliquot) to ensure that, when an "analytical error" occurs, it should be detected before a result is certified and reported by the "laboratory" performing the sample analyses (and compensated for by evaluating an appropriate number of additional "unit dose" aliquots)*, this reviewer sees no need to address "analytical error" in this guidance as opposed to true result variability because in a CGMP-compliant laboratory the reported results should only be reported and acted upon when the laboratory has certified the accuracy of the results. Returning to the commenter's suggestions, this reviewer essentially agrees with the commenter and suggests that the revised guidance contain the following language: "Identify the root cause of the failure. If the root cause is a mixing problem, we recommend that you proceed no further with implementation of the methods described in this guidance until you develop a new mixing procedure." However, this reviewer <u>cannot</u> agree with commenter's suggestion when the root cause of the failure is identified as a sampling related error and recommends the following text: "If the cause of the failure is proven to be a sampling-related problem, then take whatever root-cause-corrective actions are needed to solve the sampling-related problem and, after you verify that the root-cause-corrective actions are both valid and effective, resample the blend."	(Continued) Further, *for high dose tablets where the 80% or more of the formed dosage unit is a single active and the dosage unit weighs 100 mg or more*, you may sample at whatever sub-unit-dose weight level that your development studies has found to provide accurate estimates of the uniformity of the drug product's uniformity and is optimal for minimizing the analytical uncertainty introduced by the procedure used to sample, work up, and evaluate the sample aliquots tested. Fundamentally, for non-discrete materials, it is *scientifically sound* and "doable" for you to sample large unbiased *location-representative* multiple-dose samples that are appropriately larger in amount than the amount required for all projected evaluations *for all critical variables*, handle those samples in a manner that does <u>not</u> introduce any significant post-sampling variability changes (positive or negative) into the sample, sample duplicate unbiased unit-dose or smaller aliquots from each blend, and work up and analyze the unbiased aliquots sampled. It is **<u>not</u>** *scientifically sound* for you to use a biased sampling procedure that repetitively samples biased "1-3 dose" amounts from ever differing locations from a less than batch-representative set of general locations and attempt to attribute any "replicate" sampling as being from the same "location" or claiming that the results from replicates in the same repeatedly disturbed general location are from the same "location" or to claim that, if necessary, you can go back and sample from the same location since every sampling changes the nature of the material in that "location." [**Note:** *Even if each sampling minimally disturbs the material in the location sampled*, then it should be obvious that a sound sampling plan that disturbs each location once for 2 tests for each of four critical factors is better than one that would need to sample each location no less than 12 times!]

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# 28 Lines "224-233"	Move section under V. 1. After the word risk in line 224 add "or physically impractical (example, large blender. This reviewer does not agree with moving Lines 225-235 in the published (to the Draft Guidance file) Moreover, this reviewer suggests the following alternative to the commenter's suggested change: "This section describes sampling and testing the powder mix of ~~exhibit and process validation~~*process conformance* batches used to support implementing the ~~stratified~~ sampling ~~method~~ *plans* described in this guidance. ~~Some powder blends may present unacceptable safety risk or be physically impractical (e.g., large V-blender) when directly sampled.~~In cases where the direct sampling from the blender presents an unacceptable risk for direct sampling or such sampling is physically impractical (e.g., the manufacture should justify and use and alternative procedure for monitoring and validating the uniformity and integrity of such blends. Unless the toxicity of the active presents an unacceptable safety risk to the persons doing the sampling and no isolator-contained sampling system or robotic sampler is available, these justified sampling alternatives should be to sample from the IBCs using the sampling guidance provided in **21 CFR 211.84(c)(4)** for the sampling of components as the *minimum* for the number of levels to sample from each container. In addition, as previously discussed, the samples sampled should be sampled, handled and subsampled (*aliquoted*) for testing in a manner that ensures that the samples tested are an unbiased set that is *representative* of the blend from which the sample set was taken. Each sample should be of sufficient amount to permit the testing of at least six (6) unbiased aliquots from it for each critical variable factor (active content, active availability, weight, identity, and, where indicated, water and other impurities) that was identified as having a significant variability in development studies conducted as per Section IV.A. ~~Once described, these situations may justify an alternative procedure. In such cases, process knowledge and data from indirect sampling combined with additional in-process dosage unit data may be adequate to demonstrate the adequacy of the powder mix. In such cases, the data analysis used to justify using these alternate procedures should be described in a summary report that is maintained at the manufacturing facility~~.	This section seems to describe the general practice of sampling. It would flow better if placed as suggested, where the guidance discusses locations of sampling. This reviewer notes that the section it is currently in also addresses the final blend (powder mix) Some blender installations due to size of the blender or room considerations do not lend themselves to safe or practical sampling in the blender. In such cases sampling from drums after discharge may be justified as long as location sequence is maintained. This reviewer does not disagree with the commenter here. However, for all of the valid regulatory and sound inspection science reasons established previously, this reviewer recommends that the commenter's suggestions be modified as indicated.

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# 29 Lines 236-314	Reformat for clarity: Combine this section VI with section V, to create a 'validation' section. Rename this subsection to refer to something referring to 'in-process dosage unit uniformity (or homogeneity)' For the sound reasons cited in this reviewer's comments to the submissions of prior submitters who either suggested this course of action or, in their submission, attempted to do as this commenter suggests, this reviewer knows this should not be done – this section should remain a separate section.	The philosophy of the PQRI recommendation was to assess blend and in-process dosage units jointly, as evidenced by them being contained on the same flow diagram for the validation approach. *Whatever the PQRI's philosophy*, sound science, the precepts of the "costs of quality," and the CGMP regulations combine to make the practice proposed (use the weight corrected results from the testing of a few formed dosage units in lieu of performing any valid assessment of the uniformity of any prior non-discrete material produced during the manufacture of any batch) *not* ***legal*** *nor*, *as proposed*, ***scientifically sound*** *nor* ***CGMP compliant***. ***Moreover, assessing active uniformity is not a valid surrogate for assessing the batch uniformity of the drug product!***
# 30 Lines 240, 265	Change "normality" to "distribution of the data" This reviewer does not agree with the commenter's suggestion because the very "RSD" values they are computing are based on the assumption that the data is normally distributed. If the commenter finds that even evaluating the normality of the data is problematic, then this reviewer suggest that the commenter should propose testing the minimum number of *batch-representative* units required for a *distribution-free* assessment of the statistical properties of their samples from which they can validly project the probable limits of the active content of the dosage units in the batch for more than 99+ % of the population at a confidence level of at least 95 % (≥ 500 samples) or, failing that, use the appropriate similar range-based "AQL" estimates of distributional properties of the batch (only 230 samples). Is it perhaps that the commenter wants to remove the assessment of normality because the commenter knows that many of products have *significantly* non-normal (typically, bimodal) active content distributions because of the use equipment that is known to produce such materials (for example, "U"-shaped ribbon blenders and even those that meet their manufacturer's dimensional conformity tolerances [and few that this reviewer has seen seem to] that cannot continually recycle the significant percentage of the blend in the non-working volume [discharge valve] portion of such blenders into the working volume of the blender)? Hopefully, the Agency will disregard the commenter's baseless request.	Actually, a unimodal shape or bell-shape with short tails (high peak of data in the center) is not a 'normal' distribution, but it is a preferred shape when describing batch uniformity. A normal distribution is acceptable, but not required. To validly use normal statistics a near-normal uniform distribution of values is required – not merely acceptable. Moreover, provided a batch-representative number of samples are tested and the results found are valid, for those who lack the appropriate computer programs, normality can be assessed by simply assessing how close the mean, median, and the mode are to a) the target and b) each other; the next simplest procedure (provided a *batch-representative number* of samples has been assessed) is to plot the frequency of values against the values and visually see if the distribution appears to be normal. Similarly the closeness of the computed mean value to the target and the symmetry of the range about the target should be assessed. [**Note:** If, *for batch-representative sets of samples*, you repeatedly find that your mean for the blend is several % lower (or higher) than the computed mean for the dosage units when the dosage units are tableted at target weight or the weight-corrected results for the dosage units are compared to the blend results, then you have a sampling bias that you should eliminate and/or are inspection or material issues that need to be thoroughly investigated and resolved.]

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# 31 Line 241	Add the word 'the'. "Determine the RSD..." and remove the last 3 words from the sentence "that were developed." While this reviewer agrees with the commenter, the word "stratified" should be replaced with the phrase "dynamically sampled" to reflect sampling reality.	Clarity Since the sampling plans proposed should be "dynamic" and not "stratified," the word "stratified" should be replaced by "dynamically sampled."
# 32 Lines 243 & 282	On Line 282, change "If your test results meet this criteria for all batches, they are classified as . . ." This reviewer finds the proposed change too simplistic (**see** reviewer's "basis" remarks.).	Draft does not explicitly state that all validation batches must readily pass in order to use SCM. ONLY WHEN the results from all meet their CGMP-compliant acceptance criteria, production is at a steady rate and "REDUCED" inspection is an acceptable alternative, should the use of a valid "REDUCED" inspection plan be considered.
# 33 Line 250	Change wording to: "Prior to the manufacture of the batch, carefully identify locations... " ***For overall uniformity***, this reviewer supports the commenter and suggests the following text: "Prior to the manufacture of the batch, carefully identify ~~locations~~ sampling points throughout the compression or filling operation to sample your in-process dosage units. Your selection should be done in a manner that ensures the points selected encompass the dosage-forming phase of the manufacture of the batch. The sampling locations should also include significant process events (such as**,** hopper changeover~~,~~ and hopper filling**,** ~~or~~ machine shutdown and restart, and the beginning and end of the compression or filling operation~~.~~[16]) that are outside of the dosage-forming machinery's normal operating envelope. There should be at least 20 locations ~~with 7 samples each for a minimum total of 140 samples~~ at which you sequentially sample a number of dosage units that is some integer multiple of the dosage-unit forming stations in the system being studied for a minimum total of not less than 600 units for *each variable factor* that needs to be evaluated ~~for~~ to comply with the representative sample sampling requirements of the drug CGMP regulations (**21 CFR 211.160(b)(2)**). In general, the samples at each sampling point should be placed in a suitable separate labeled container. These include periodic sampling locations and significant-event ~~locations~~ sampling points**.** [16] The beginning and end samples are taken from dosage units that would normally be included in the batch." (Consider adding a cross-reference to Section IV-B as the recommended approach.) This reviewer sees no reason to make this change. **Rationale for the Parenthetical Comment:** The commenter offered no rationale here (Continued on next page)	Current wording does not explicitly state that sampling locations should be determined "prior" to the validation exercise, as PQRI proposal does. **Commenter's First Statement:** In the planning process for the dynamic sampling of a production phase, the sampling needs to be defined in terms of "*points*" rather than "locations." [**Note:** This is the case since the ***location*** of the sampling remains fixed and the sampling points are separated by time rather than location.} *While this reviewer has no problem with the total number of points*, valid unbiased "*process representative*" dynamic sampling requires the sampling of not less than one dosage unit from each dosage-forming station at each point. Typically, because the samples collected are used for both variable factor testing and attribute factor examination, some integer multiple of that number of dosage units is sampled at each sampling point. Because the manufacturer needs to be highly confident (a confidence level of 95% or higher) that their findings are truly predictive of the results that would be found if the entire batch were tested, NLT 200 *batch-representative* units (made up of an equal number of randomly selected units from the *process-representative sample* of units collected at each point) must be tested for the single variable factor, active content, being addressed in this guidance. The need for testing such a 200-unit sample is dictated by: a. The lack of rigorous controls on each of the physical properties that affect the uniformity achieved each time a defined processing step set is performed using components whose properties vary in a complex undefined manner. (Continued on next page)

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# 33 Line 250 (Continued)	(Continued) _____ **Reviewer's Basis for Rejecting Commenter's Suggestion:** Since Section VI and the prior ones logically proceed from subsection to subsection, there is no need to add further logical clutter by adding a parenthetical reference to the next subsection in the current subsection.	(Continued) b. The need for a confidence level of 95 % or higher in the validity of the estimation of the acceptability or non-acceptability of the batch at the end of this process phase. c. The numbers required by the applicable recognized statistical consensus standards ("**ISO 3951**" or "**ANSI/ASQC Z 1.9**") for evaluating batches of discrete units for the normal inspection, "process variability unknown—SD" case, and d. A lack of sufficient production history to justify the use of a hierarchical sampling plan that initially tests a consensus-standard-recognized defined subset (50 *representative* units in this case) and then proceeds in different pre-established manners depending upon the outcome observed for the initial subset tested.
# 34 Lines 257-258	At the end of the bullet, add: Assay all 7 per location if required in Section V. Though this reviewer does not support this addition, this reviewer does recommend revising the cited **Lines 258-259** in the published Draft to: " • ~~Assay at least 3 of the 7~~ *For a 20-point sampling, select, at random, 10 units from each sample point, weigh each, work up each unit in a manner that preserves the link between each unit's identity and its weight, appropriately test the each worked up sample, determine the results for each sample,* ~~and~~ weight correct each result *and appropriately tabulate the results found.* (**Note:** ***Should you wish to evaluate a lesser number***, ~~T~~the number of samples to evaluate from each sampling point should be specified and justified for a given product and process.)"	There is no connection back to the performance of the blend (Set V). If one has to assay 7 per location to satisfy blend homogeneity, the same samples may be used to demonstrate in-process performance. Since this section (Section VI) discusses the "verification" of the adequacy of the blend specifications as established for full-scale conformance batches for the single critical variable factor uniformity, "active uniformity," the evaluation should require the assessment of not less than 200 batch-representative dosage units appropriately selected for the samples at each sampling point. As with all *scientifically sound* inspection plans for materials made in batches, a body of consistently conforming outcomes is needed before any reduction in the inspection level (number) can be justified (typically not less than ten (10) consecutive successful "routine production" batches after not less than "3" consecutive successful "initial process conformance batches").
# 35 Between 258 & 259	Add : • Analyze the dosage units according to the flowchart in Attachment I. This reviewer does not agree with the commenter's suggestion and recommends that this change not be made.	There is no connection back to the flowchart in Attachment 1. The PQRI document provides acceptance criteria for the stage 1 data (3 per location) and also provides stage 2 sample sizes and acceptance criteria, if needed. See this reviewer's remarks in Row "VI - A '257-258'"

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# 36 Amendment line number 260 (new text)	Change to "Conduct an analysis of the dosage unit stratified sampling data to assess the active ingredient distribution throughout the batch (e.g., visual assessment of a histogram or a probability plot). Indications of trends, bimodal distributions, or other forms of a distribution other than bell-shaped should be evaluated." Though this reviewer agrees with the commenter that this bullet point needs to be revised, this reviewer suggests it be changed to: "• Conduct an analysis of the dosage–unit ~~stratified~~ dynamic sampling ~~data~~ weight-corrected results to demonstrate that the results obtained for the *batch-representative samples* tested indicate that the dosage units in the batch probably ~~has~~ have a *near* normal active-content distribution ~~of active ingredient~~. At the simplest level, one can determine the mean, median and mode values for the data set – when they are, within the observed result uncertainty, the same, the level of active in the batch of tablets can be presumed to be normally distributed. If this simple test is inconclusive, then you should construct a frequency bar graph depicting the frequency of values in a given narrow value range interval on its "Y=axis" against the mean active level in the interval increments specified on the "X-axis," and examine this chart and the tabulation of the results versus time point. Indications of trends, bimodal distributions, or other forms of a distribution other than normal should be investigated. If any of these ~~occurrences~~ conditions significantly affect your ability to ensure batch ~~homogeneity~~ uniformity of the active(s), ~~they should be corrected~~ the root cause or causes for the non-uniformity of the results should be identified, appropriate corrective actions implemented, and the studies repeated until the results indicate that the batch is sufficiently uniform with respect to the level of active in the dosage units."	Actually, a unimodal shape or a bell-shape with short tails (high peak of data in the center) is not a normal distribution, but it is a preferred shape when describing batch uniformity. A normal distribution is acceptable, but not required. The commenter's rationale again misstates the reality that a normal distribution is the preferred distribution but that many near-normal unimodal or bell-shaped distributions are acceptable distributions where it is valid to use "normal" statistical procedures to describe the approximate dispersion of the critical variable factors' results about the calculated average value and predict the batch's dispersion of these critical variable factors, including the active(s) about the batch's targeted mean value. The critical caveats are: a. The *samples tested* must be *representative* of the *batch* and b. The *number tested* must be sufficient to provide a high level of confidence (typically, at the 95 % confidence level or higher) that the outcomes observed for the samples tested do, in fact, reflect the expected outcomes for the *untested units* in the *batch*. For the initial "full scale" conformance batches to which this procedure applies, the minimum number that should be tested is NLT 200 *batch-representative* dosage units.

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# 37. Line 265	Change "normality" to "distribution (e.g., unimodal, bell-shaped, normal)" *Provided the text is changed to order the types of distributions from the most acceptable to the worst and include distributions for which the procedures shown are not appropriate*, this reviewer supports replacing "normality" with "distribution (e.g., …)." This reviewer suggests: Change 'normality' to 'distribution (e.g., normal or Gaussian, skewed Gaussian, bell-shaped, Poisson, unimodal, bimodal, rectangular, wedge-shaped, hyperbolic, disjoint)' in line 266." In addition, the bullet point containing the first change should be revised to: "• Prepare a summary of this analysis. ~~Potential i~~Investigation results along with a description of batch ~~normality~~ distribution (e.g., normal or Gaussian, skewed Gaussian, bell-shaped, Poisson, unimodal, bimodal, rectangular, wedge-shaped, hyperbolic, disjoint) should be included in ~~the~~ this summary. ~~Submit~~ For your drug product submissions to the Agency for review, you should include the results' data and this summary with the ~~application~~ submission as described in section VIII of this guidance."	See comment number 36 above. The proposed change should include examples of distributions that are unacceptable as well as those that are or may be acceptable. In addition the text associated with this bullet point also needs to be revised as shown.
# 38 Line 268	Remove the phrase "In addition to this analysis of batch normality" and replace with "Additionally, we recommend..." Change "normality" to "distribution (e.g., unimodal, bell-shaped, normal)" This reviewer supports the commenter's suggestion, but understands that the rest of the sentence also needs to be revised to: "~~In addition to this analysis of batch~~ Additionally, *provided the results obtained are acceptable*, we recommend that you analyze the batch's distribution (e.g., normal or Gaussian, skewed Gaussian, bell-shaped, Poisson, unimodal, bimodal, rectangular, wedge-shaped, hyperbolic, disjoint) and that you classify the test results as *readily ~~pass~~ passing, ~~or~~ marginally ~~pass~~ passing* or *failing* according to the following procedure:"	See comment number 36 above. The text changes proposed should include restricting the classification to those active content result sets that indicate the batch has an acceptable active uniformity. When the results are unacceptable, you should initiate the appropriate in-depth "root cause" investigation and, when the cause(s) is(are) identified, implement the appropriate "root cause" CAPA plan before proceeding with the classification scheme proposed. The second proposed change should include examples of distributions that are unacceptable as well as those that are or may be acceptable as reflected previously in commenter's **Comment 37**.

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# 39 Line 273	Change to "For each separate batch, compare the weight-corrected test results to the following criteria:" This reviewer cannot agree with the commenter's suggestion because it is at odds with the clear in-process CGMP requirements that require the active's dosage-unit uniformity to be evaluated on "**the characteristics of in-process material**" the weight-corrected active is NOT a characteristic of the in-process dosage units – it is a biased characteristic, and suggests the following CGMP-compliant alternative: "For each ~~separate~~ *individual* batch, compare the dosage-unit test results to the following criteria:" In addition, the rest of this section (Lines 276-285) should be revised to: "• For all individual results **for each active individually** (for each batch**,** n ≥ ~~60~~ **200**)**,** the overall RSD ≤ ~~4.0~~ **2.5** percent." • "For all individual results **for each active individually** (for each batch**,** n ≥ 200)**,** the overall mean percent of the target value should be not less than the target value percent. In practical terms, this requirement translates into: **$[\bar{x}_n + (t_{(0.975,n-1)} \times RSD/\sqrt{\{n-1\}})]\ \% \geq Target_{Process}\ \%$.** • Each ~~location~~ sampling-point mean is within the relative range of ~~90.0~~ **≥ 93.0** percent to ~~110.0~~ **≤ 107.** percent of target strength. • All of the individual results are **appropriately** within the relative range of ~~75.0 ≥~~ **85.0** percent to ~~125.0 ≤~~ **115.** percent of the target strength or, ***failing that***, not more than 1 in 200 (tablets) [or 2 in 200 (capsules)] tested are outside of 85.0 percent to 115. %, and none are outside of the relative range of 80.0 % to 120 % of the target strength. • The results meet the batch acceptance criteria for your established AQL level when the results are evaluated against the 'process variability unknown—standard deviation' criteria for 'normal inspection' in ISO 3951 (or ANSI Z1.9, its American equivalent). If your test results meet all of these criteria, ~~they are~~ the active results can be classified as *readily ~~pass~~* passing and, *provided you have adequate controls on all of the physical properties of the components in your formulation, all of the data for the development and the other initial conformance batches supports the batch-to-batch reproducibility of the results obtained*, you ~~can~~ may be able to start routine batch testing using the Standard ~~Verification~~ Classification Method (SC~~V~~M) described in section VII. If your test (Continued on next page)	Clarification for those not familiar with the PQRI proposal. **21 CFR 211.110(a)**, "…Such control **procedures** shall be established to **monitor the output and to validate** the performance **of** those manufacturing **processes** that **may be** responsible for **causing variability in the characteristics of in-process material** and the drug product. All that the *weight-corrected formed dosage-units active-content results* should be used for is to compare the *weight-based blend results* to the *weight-corrected formed-dosage units results* in instances where such comparisons are valid – this is clearly not the case here. **For RSD:** For a batch to be characterized as "readily passing," all of the results found should be within the **USP**'s "any article" *expectation range* and not just its lifetime "none" range. This is the case because the batch percentage tested is typically less than 0.1%. Thus, almost all results must be inside of 85 % to 115 % of the permitted target because finding any outside of that range clearly establishes that, post release, some sets of 30 may fail the **USP**'s "post release" uniformity criteria by having more than 1(for "tablets") or 2 (for "capsules") outside the expected range, and, if such 30's are tested, the batch will fail. **For Set Mean:** A critical CGMP-compliance issue (that the Draft seems to ignore) is whether or not the overall mean is sufficiently close to the target level to ensure that batch meets the CGMP requirement set forth in **21 CFR 211.101(a)**. **For Sampling-Point Means:** As stated previously, the samples are from different time points not from different locations. Moreover, since the expectation for all individuals in small samples should be that they are mostly in the relative range from 92.5 % to 107.5 % (based on the RSD for this category), the means expectation range should be inside of the expected values range. Furthermore, the mathematical precision should be the same for both limits **For Individual Active's Results:** For a batch to be characterized as "readily passing," almost all of the results found must be within the **USP**'s "any article" *expectation range* and not its lifetime "no units outside of" range. (Continued on next pages)

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# 39 **Line "273"** (Continued)	(Continued) results fail to meet any of these criteria, we recommend that you test additional samples from the set of samples sampled and compare the results found for the combined sets with the *marginally ~~pass~~* passing criteria described below." [**Note:** The importance of meeting the "85 % to 115 % of target" range cannot be over emphasized.]	(Continued) This is the case because the tested % of the batch is typically less than 0.1%. In such cases, all results should be inside of 85 % to 115 % of the permitted target because finding any outside of that range clearly establishes the reality that, post release, some sets of 30 in the batch may fail the **USP**'s content uniformity criteria by having more than 1 (for "tablets" or 2 ("for capsules") outside the expectation range, and, should such 30's be tested, the batch will fail.
# 40 **Line "277"**	Add a space between "to" and "110.0" This reviewer agrees.	typo
# 41 **Lines**	Change to "If your dosage unit test results fail to meet the criteria for the readily pass classification, compare the weight corrected test results to the following criteria:" This reviewer cannot support the commenter's suggestion because it conflicts with clear in-process CGMP material assessment requirements that require the ***characteristics*** of the material to be assessed, not some "*weight-variability corrected*" *characteristic* as the commenter is again proposing. Provided the Draft is revised to limit the scope to the content uniformity of the active, this reviewer suggests the following CGMP-compliant alternative: "If your dosage unit test results fail to meet the criteria for the r*eadily passing* classification, you should first investigate the findings to see if there are any processing factors associated with a given sampling point that may have cause the data at that point to one or more results that either caused the batch not to meet a given "readily passing" criterion. This is especially important in cases where the problem point or points are associated with "significant events," (like the start of dosage unit formation or the end of dosage-unit formation or an equipment-related interruption and restart), where the procedure may easily be changed (for example, changing the end of formation point from "after the last of the final blend has been loaded into the hopper, continue running until the level of blend in the hopper reaches the '25 %' full mark" to "after …into the hopper, continue running until the level … reaches the '50 %' full mark) to reduce the risk of an excursion. If any valid result is outside of the range from 75 % to 125 % of target, all that you should do is investigate and revert to the formulation development stage because the current process obviously does not reliably produce in-process units that meet the CGMP minimums. ***In some cases***, (Continued on next page)	To comply with Amended line 283, which describes how many to test. Plus, clarify the data are weight corrected for those not familiar with PQRI proposal. This reviewer already addressed this issue in his basis statements in **Comment 39**. When one finds results outside of those expected, the first thing that they should do is review the results and look to see if the unexpected results have a possible cause that can be addressed by a change in procedure. For example, if the most of the results for "Point 22" are much different that the results found for "Point 21" or "Point 23" and "Point 22" corresponds to a "significant event" such as "restart after tooling change" look to see what can be done to change the restart procedure and/or the point at which formed dosage units are again collected as part of the batch that could reduce the risk of including such "different" units into the batch of dosage units suitable for further processing. However, unlike the **USP**'s "grab sample" approach (directly applicable **only** to "in commerce" drug product) where one can justify the relaxation of the acceptance criteria for sample average properties like the mean and the RSD when the testing is expanded from one level of units to a larger number of units, sampling that complies with the CGMP should yield results that give "mean" and "RSD" values that are respectively: a. Closer to the target level and b. Smaller or certainly not larger than the value found for the smaller number of ***batch-representative*** samples tested. Thus, to even propose to widen the RSD for acceptability, those that wrote the Draft are (Continued on next page)

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# 41 Lines "289-291" (Continued)	(Continued) you may be able to justify evaluating ~~assay the remaining dosage units (all 7 units per location)~~ another set of dosage units and ~~compare~~ comparing the test results for the combined sets to the following criteria:"	(Continued "admitting" that the sampling and testing plans they propose do not reflect the CGMP minimum requirement that both must be *representative of the batch*. Moreover, during criteria verification it is important to increase testing whenever the initial testing results do not meet the *scientifically sound sample specifications* and *batch acceptance criteria*.
# 42 Line 293	Change to: "…results (for each batch n > 60) the …" This reviewer cannot support the commenter's suggestion. This reviewer offers the following inspection-science-based, CGMP-compliant alternative: "If your dosage unit test results fail to meet the criteria for the r*eadily passing* classification, you should first investigate the findings to see if there are any processing factors associated with a given sampling point that may have cause the data at that point to one or more results that either caused the batch not to meet a given "readily passing" criterion. This is especially important in cases where the problem point or points are associated with 'significant events,' (like the start of dosage unit formation or the end of dosage-unit formation or an equipment-related interruption and restart), where the procedure may easily be changed (for example, changing the end of formation point from 'after the last of the final blend has been loaded into the hopper, continue running until the level of blend in the hopper reaches the 25%- full mark' to 'after …into the hopper, continue running until the level … reaches the 50%-full mark') to reduce the risk of an excursion. If any valid result is outside of the range from 75 % to 125 % of target, all that you should do is investigate and revert to formulation and process development since the current process does not reliably produce in-process units that meet the CGMP ***minimums***. ***In some cases***, you may be able to justify evaluating ~~assay the remaining dosage units (all 7 units per location)~~ another 200-unit batch-representative set of dosage units and ~~compare~~ comparing the test results to the following criteria:" • For all individual results (for each batch, n ≥ ~~140~~ *400*), *the overall* RSD ≤ ~~6.0~~ *2.5* percent." • For all individual results (for each batch, n ≥ 400), the overall mean percent of the target value should be not less than the target value percent. In practical terms: $[\bar{x}_n + (t_{(0.975,n-1)} \times RSD / \sqrt{\{n-1\}})]\ \% \geq Target_{Process}\ \%$. (Continued on next page)	Must be for each batch. - Clarification This is the case because the commenter's suggestion does not test an adequate number of batch-representative units that is appropriate for conformance batches that typically contain more than 250,000 dosage units, especially when the initial testing does not meet the Draft's *readily passing* criteria. When one finds results outside of those expected, the first thing that they should do is review the results and look to see if the unexpected results have a possible cause that can be addressed by a change in procedure. For example, if the most of the results for "Point 22" are much different that the results found for "Point 21" or "Point 23" and "Point 22" corresponds to a "significant event" such as "restart after tooling change" look to see what can be done to change the restart procedure and/or the point at which formed dosage units are again collected as part of the batch that could reduce the risk of including such "different" units into the batch of dosage units suitable for further processing. However, unlike the **USP**'s post-release, any "grab sample" (*article*) approach where one can justify the relaxation of the acceptance criteria for sample average properties like the mean and the RSD when the testing is expanded from one level of units to a larger number of units, sampling that complies with the CGMP should yield results that give "mean" and "RSD" values that are respectively: a) closer to the target level and b) smaller, or certainly not larger, than the value found for the smaller number of batch-representative samples tested initially. Thus, to even propose to widen the RSD for acceptability, those that wrote the Draft are "admitting" that the sampling and testing plans they propose do not reflect the CGMP minimum requirement for that both must be representative of the batch. (Continued on next page)

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# 42 **Line 293** (Continued)	(Continued) • Each ~~location~~ sampling-point mean (for 20 units chosen at random from the number collected at each sampling point) is within ~~90.0~~**94.0** percent to **106.**~~110.0~~ percent of target strength. • All individual results are within the range of 75.0 percent to 125.0 percent of target strength, not more than 1 tablet (2 capsules) in the 400 tested is outside of the range from 80 % to 120 % pf the target strength, not more than six (6) tablets (18 capsules) in 400 units tested is outside of the range from 85 % to 115 % of the target strength, and no test point of 20 contains more than one (1) tablet (two [2] capsules) that is outside of the 85 % to 115 % range. • The lesser of $\|115. - \bar{x}\|$ or $\|\bar{x} - 85.0\|$ divided by ($3.27 \times RSD_{n=400}$) is not less than 1.5. "If your test results meet these criteria, ~~results~~ the *batch* can be classified as *marginally* ~~*pass*~~ *passing*. If your samples do not meet these criteria, we recommend that you investigate the failure, find justified and assignable cause(s), correct the deficiencies, and repeat the powder mix homogeneity assessment, in-process dosage unit sampling ~~correlation~~ comparison, and initial criteria establishment procedures. The disposition of batches that have failed the m*arginally pass* criteria is outside the scope of this guidance. However, because these are not "*passing*," the CGMP regulations in **21 CFR 211.110** clearly require such materials to be rejected (**21 CFR 211.110(c)** 'In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.') and quarantined (**21 CFR 211.110(d)**, 'Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.') until their deficiency or deficiencies can be corrected."	(Continued) **For RSD:** For a batch to be characterized as "marginally passing," the representative samples' active content results' $RSD_{n \geq 400} \leq 2.5$ %. **For Sampling-Point Means:** As stated previously, the samples are from different time points not from different locations or sampling intervals. Moreover, since the expectation for all individuals in small samples should be that they are within the relative range from 92.5 % to 107.5 % (based on the RSD for this category), the means expectation range should be inside of the expected values range and slightly narrow as the number of sample aliquots tested increases. **For Individual Active's Results:** For a batch to be characterized as "marginally passing," most of the results found should be within the **USP**'s "any article" *expectation range* and not its lifetime "no units can be outside of" range. This is the case because the tested % of the batch is typically less than 0.1%. In such cases, most all results must be inside of 85 % to 115 % of the permitted target because finding more than 15 tablets (42 capsules) in 1000 outside of that range clearly establishes the reality that, post release, some sets of 30 in the batch MAY fail the **USP**'s content uniformity criteria. **Batch Acceptance Criteria:** This reviewer notes that the Draft failed to mention, much less address, the issue of setting acceptance criteria for the ***batch*** based on the results found from the testing of a small percentage (currently, less than 0.2 % and in an increasing number of cases less than 0.02 %) of the batch even though such acceptance criteria are clearly needed and, for the drug product units tested for acceptance for release, are explicitly required (**21 CFR 211.165(d)**). **After all, it is the untested part of the batch that the patients will be prescribed.** To address the Draft's omission, this reviewer has provided corrective language.

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# 43 Line 314	There is no mention about including the beginning and end of the batch in the 10 locations for stratified sampling. Is this intentional? Since this document is guidance, the text clearly leaves it up to the manufacturer to define the sampling points across the batch. However, this reviewer recommends the text here be revised to read: "You should identify **and designate** ~~at least~~ ~~10~~ **not less than 10 'routine production'** sampling ~~locations~~ **time points (the start point, the end point, and not less than 8 approximately evenly spaced intermediate points)** during capsule filling or tablet compression ~~to represent~~ **that your studies have established to be *representative of*** the entire routine manufacturing **of the formed units that comprise the** batch **while making provision for the inclusion of any 'significant events' that may occur during this production step. In addition, the number sampled at each point should be appropriately adjusted to be that integer multiple of all of the dosage forming stations in the forming system that is required to satisfy all of the firm's pre-established sampling and sample evaluation (examination and testing) for the said formed units**."	The PQRI proposal specifically states that the beginning and end of the batch should be included in the 10 locations for routine testing (pp 8-9 of IS). This reviewer again notes that the samples should be classified as "sampling point" samples, and not, as the Draft (and the commenter did not object to) "locations." Moreover, the use of the terms "interval sampling" or "interval samples" should be discouraged because that wording is only appropriate when the samples are continually collected across an interval instead of at a specific point in time.
# 44 Line 319	Delete the word "the" that precedes "routine". This reviewer agrees with the commenter that the word "the" preceding "routine" can be deleted.	Clarity The stated article, "the," is superfluous.

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# 45 Line 337	In addition to the amendment text, add another bullet: • Previous routine test was per SCM and passed SCM criteria. This reviewer cannot agree with the commenter's suggestion because it is a needed but incomplete change – much more is needed. Provided the guidance is corrected to conform with all of the clear requirement ***minimums*** of the applicable CGMP regulations, the sample number minimums are corrected to "50 batch-representative dosage units" for 'SCM' and "200 batch-representative dosage units" for 'MCM,' and the statistically flawed switching rule for switching from 'SCM' to 'MCM' based on a single excursion is corrected, this reviewer does supports changing the switching rules as follows: "Use 'SCM' criteria your basis Inspection Plan when: 1. The initial process conformance batches have established that, under certain conditions, a "reduced" inspection plan can be used. 2. Production is at a steady rate. 3. Your initial, post-conformance studies have produced more than 10 consecutive batches that met the 'MCM' criteria and you are authorized to switch to an 'SCM' plan. 4. The routine test for the previous batch was 'SCM' and passed 'SCM' criteria. 5. Your current campaign consists of at least 10 consecutive batches and the routine test for the previous 5 batches was 'MCM,' but each batch met the 'SCM' criteria."	3 scenarios to use SCM exist in PQRI document: 1. Validation was readily pass and we are just starting production 2. Routine test method is SCM and we continue this as long as we keep passing. 3. Routine method is MCM, but switching rule is met. This draft and the commenter seem to have recognized this when they require not less than 5 consecutive batches that are tested using a "full" set but pass the "reduced" set criteria before switching from 'MCM' to 'SCM.' However, the proposed rule for 'SCM' to 'MCM' has no such valid provision. Furthermore, before a "reduced" inspection plan (the 'SCM' plan here) can validly be considered for implementation, the valid use of any "switching rules" in inspection requires (based on the controlling guidance provided in applicable recognized consensus standards, ANSI Z1.9 (and ISO 3951): 1. Production to be at a steady rate, and 2. Initially, at least 10 batches have been inspected using the normal inspection plan (the 'MCM' plan here) without any being rejected. Thus, unless the production process: a) continually produces batches without interruption, or, when production is intermittent, b) produces more than ten (10) batches in each campaign the use of any reduced ('SCM') inspection is, at best, difficult to justify. Yet, this reviewer notes that this guidance failed to mention much less address the preceding realities. Finally, for those who claim that testing "200" is onerous in batches upwards of 250,000 in size should note that the number in question is less than 0.1 %! (1 in a 1000) of the units in the batch for such batches and less than 0.01 % (1 in 10,000) for batches larger than 2,000,000 dosage unit (a "batch size" that is becoming increasingly common today – a size that should soon trigger a revision to said consensus standards since their current tables end with sizes of 150,001 to 500,000 and 500,001 and over, the table needs at least one (1) more level (probably at 2,000,000 as follows: Replace: "500,001 and over" with: "500,001 to 2, 000,000," and Add: "2,000,001 and over."

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# 46 Lines "354-355"	Change the first sentence to the same wording used in the first sentence of 368-369. This reviewer does not agree with the commenter's suggested change and recommends that the first sentence in Lines 369-370 be changed to read the same as the first sentence in Lines 355-356, "If the results pass these criteria and the adequacy of mix and uniformity of the dosage unit content for the batch are adequate, you can use the SCM for the next batch."	The first sentence should be the same; so the difference in wording is confusing. Line 368 is written more clearly. Based on the stated scope of this guidance, *general (final) blend and dosage-unit uniformity of the batch*, the first sentence in Lines 355-356 is the obviously more correct wording. Written in this manner, the guidance at least recognizes that the mix adequacy and the dosage-unit uniformity for the other critical variable factors must be also found to be "adequate" before a valid decision can be made as to how to proceed for the next batch. Thus, the first sentence Lines 369-370 should be changed to be the same as the first sentence in Lines 355-356.
# 47. Line 366	Add the following bullet following Line 366: • All samples within 75%-125% of label (not corrected for dosage form weight) This reviewer agrees with the commenter that this bullet is required.	Without this statement, it is possible that a core (uncoated) tablet could exceed 75% - 125% of label and still pass the routine criteria. If CU testing for compendial requirements is being done on the coated product, and if this did not again occur, this batch would technically meet all requirements.
# 48. Lines 375-376	Change "either... is met" to "any...are met" This reviewer agrees with the substitution of "any" for "either" but that the verb change to "are met" should not be made.	The commenter provided no rationale for this change. Use here "any" is clearly denotes the singular condition's being controlling.
# 49. Line 382	In addition to the amendment text, add another bullet: • Previous routine test was per MCM and passed MCM criteria This reviewer cannot agree with commenter's suggestion here because, as stated for the 'SCM' case, it is insufficient. Provided the same caveats that are stated for the case for the 'SCM' criteria are accepted here, this reviewer proposes the following 'MCM' criteria: "Use 'MCM' criteria as your basis Inspection Plan when: 1. The initial process conformance batches have established that a 'NORMAL' inspection plan should be used. 2. You are just starting production and have not yet produced more than 10 consecutive batches that met the 'MCM' criteria. 2. You do not produce more than 10 batches in any run or campaign. 3. Routine testing for the previous batch was 'MCM,' or (Continued in adjacent column➔)	3 scenarios to use SCM exist in PQRI document: 1. validation was marginally pass and we are just starting production 2. routine test method is MCM and we continue this until we can switch. 3. last batch started as SCM, but had to go to MCM pass The basis for this set of 'MCM' criteria is stated in the previous section on the 'SCM' criteria. (➔ Continued from previous column) 4. Routine test for the previous batch was started under 'reduced' inspection ('SCM'), but had to be inspected under a "normal" inspection plan ('MCM') or an augmented inspection plan (not provided in this guidance) and this is the third such occurrence in the last 5 consecutive acceptable batches. 5. The previous batch was rejected. 6. The previous five (5) batches were inspected under an 'augmented' sampling plan (not provided) and met the 'MCM' criteria."

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#50 Line "383"	Add sample size: "...from Stage 2 SCM (n ≥ 30) analysis..." This reviewer does not agree because, *even with the commenter's proposed addition*, the guidance provided is not based on the taking of a *batch-representative sample* and the *number* of units *tested* does not meet the *scientifically sound* and *appropriate* requirements of the CGMP regulations.	For additional clarification The guidance proposed is not *scientifically sound* and does not meet the clear CGMP minimums that are applicable to in-process materials and the in-process drug product.
# 51 Line "384"	Change "Marginal Verification Method (MVM)" to "Marginal Criteria Method (MCM" While this reviewer agrees that this change would improve the consistency of the naming conventions being used, this reviewer notes that the guidance provided does not comply with the CGMP minimums established for the inspection (sampling plans and testing procedures) requirements set forth in **21 CFR Part 211**.	Correction Even though the clear applicable CGMP requirements set forth in **21 CFR Part 211** require *representative sample* inspection of sufficient samples to permit the prediction of the characteristics of the batch tested from the sample results obtained, the guidance set forth in this Draft does not meet these requirement ***minimums***.
# 52 Line "390"	Add 1 word: "We recommend that all results obtained from analysis…" While this reviewer agrees with the commenter that adding the word "obtained" improves the accuracy of what is being stated, the guidance provided still is not CGMP compliant.	Clarification See reviewer's basis remarks in the previous row, **Comment 51**.
# 53 Amendment line number "395" (new text)	Minor changes to last sentence: "That is, to establish justified assignable cause(s), take necessary corrective actions, and if appropriate, repeat the powder mix assessment, stratified sample correlation, and initial criteria establishment procedures." This reviewer cannot and does not support the changes proposed here. However, this reviewer does agree that the text needs to be improved and suggests the following: "When a batch fails, *in addition to an investigation into that batch's failure*, the firm must also investigate all associated batches, released or not." Moreover, any *scientifically sound* CGMP-compliant inspection plans (the CGMP's *sampling plans* and *test procedures*) must include a switch to more intensive inspection whenever there is a repeated real failure of a batch and, when unexpected results are obtained, also switch to more intensive inspection whenever this unusual pattern occurs. [**Note:** The consensus standards (ANSI Z1.9 and ISO 3951) provide a simplified discussion of this in subsection entitled "**NORMAL, TIGHTENED, AND REDUCED INSPECTION**."]	If a single lot fails SCM and MCM, and the root cause is identified to be due to a deviation from the validated process (say materials were not added in correct order), we do not want to have to go through revalidation of all the correlations, just reject the lot and put measures in place to prevent recurrence. But, if the process is 'broken' and must be fixed, then this all needs to be done Since validation is an ongoing, a failure cannot require a "revalidation." Moreover, the commenter has deliberately mischaracterized the proposed changes, as minor changes, when, in fact, *as the commenter's rationale clearly reveals*, the commenter knows that the proposed changes are major changes. However, *under the law*, the test must be changed to conform to the applicable CGMP minimums. Since this Draft is a guidance document, it compels nothing. (Continued on next page)

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# 53 Amendment line number "395" (new text) (Continued)		(Continued) Moreover, under CGMP, the judgment permitted to the manufacturer is exactly how to meet the clear requirement *minimums* stated in the regulations – ***compliance is required*** and ***knowing non-compliance subjects those who do to the risk of prosecution under the appropriate statutes as well as renders any batches produced in a non-complying manner adulterated***. [**Note:** Based on the commenter's remarks, the commenter is either unaware of the regulations and thus unqualified under CGMP (**21 CFR 211.25**) or supporting the knowing non-compliance with the CGMP and, *if the later is the case*, conspiring to subvert the regulatory process.]
# 54 Line "396"	Or adapt at, in or on-line measurement systems to ensure adequate powder mix assessment. *While this alternative may be a solution*, in general, it can only be a viable solution when the blends are mechanically stable uniformly structured mixtures of solids – which is not generally the case when classical sampling procedures have the types of difficulties alluded to in this text. [**Note:** Even the recently published approaches using a single set of a 3-component mixture and only watching some aspect of "component variability," while elegant and interesting, fails to show more that an equilibrium is established – not that the mixture is adequately uniform. Moreover, the article fails to show that repetitive runs using mixtures from different lots converge to the same values.]	PAT initiative in Line 71 Based on this reviewer's limited experience with the NIR systems upon which the thrust of the PAT initiative seems to be founded, this reviewer does not understand how the training problem will be "solved" when the requisite training set are complex "mechanically unstable" mixtures of multiple not-well-characterized components that, *based on their intrinsic complexities*, would be required to number in the hundreds if not thousands to cover the variability range and interactions for the components in such mixture – not to mention the problem of time-separated "replicate measurements" under varying environmental conditions. (← Continued in next column.)
# 55 Line "404"	Change "...criteria and result in RSD..." to "criteria and for each batch the RSD..." This reviewer accepts that the change does clarify the situation.	Clarification. This has currently been misread that ail batches are combined together to get RSD. Each batch RSD must meet this.
# 56 Line "416"	(CCTD17 3.2P.3.3). Replace with P.3.4 This reviewer leaves this issue up to Agency.	Drug Product Draft Guidance January 2003 lists controls for critical steps under P.3.4
#57 Delete "418-420"	Replace with: Methods that will be used to demonstrate the adequacy of powder mix. This reviewer does not agree with the commenter's proposal and recommends that the changes proposed not be made.	It is not customary to place detailed descriptions of sampling plans in the drug product application. These are- compliance issues and can be examined by the investigator at the PAI. Since the Agency has the right to require that any and all information be submitted and in light of the Agency's current make up, this reviewer knows that the requested information should be submitted and supports the Agency's request for its submission.

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# 58 Delete "421-426"	Replace with: Data that confirms suitability of the powder mix and dosage product uniformity This reviewer does not agree with the commenter's proposal and recommends that the changes proposed not be made.	Once again the detailed requirements for data presentation in an application are inappropriate. Since the Agency has the right to require that any and all information be submitted and, *in light of the Agency's current make up*, this reviewer knows that the requested information should be submitted and supports the Agency's request for its submission.
# 59 Lines "423-424"	Change "demonstrating a normal distribution" to "evaluating the distribution" This reviewer does not agree with the commenter's proposed change and recommends that, *at a minimum*, this bullet be changed to read: "● Summary of the in-process dosage unit dynamically sampled test results analysis that includes an evaluation of the distribution of the result values observed for each critical variable factor that establishes that said distribution is uniform and mono-modal."	A normal distribution is acceptable, but not required. This reviewer suggests that the more valid rationale statement is "While a normal distribution is desirable, all that is generally required to ensure batch uniformity is that the distribution for each critical variable factor, including the active, should be uniform and mono-modal.
# 60 "429"	(CTD 3.2.P.4.1) Replace P.5.1 This reviewer leaves this issue up to Agency to resolve.	P.5.1 applies to specifications for drug products
# 61 Delete Lines "431-433"	Replace with: Test procedures and acceptance criteria for finished product uniformity of content. This reviewer does not agree with the commenter's proposal and recommends that the changes proposed not be made.	Here to the detailed requirements for data presentation in an application are inappropriate Since the Agency has the right to require that any and all information be submitted and in light of the Agency's current make up, this reviewer knows that the requested information should be submitted and supports the Agency's request for its submission.
# 62 Line "436"	(CTD 3.2.P.2.2) Replace with P.2.3 This reviewer leaves this issue up to Agency.	P.2.3 applies to manufacturing process development.
# 63 Lines "438-442"	Replace with: Data that relate powder mix uniformity, in-process dosage uniformity and finished product uniformity This reviewer does not agree with the commenter's proposal and recommends that the changes proposed not be made.	It is recognized that powder mixing is a critical step but statistical correlation is not required to show adequate control and goes beyond the requirements presented earlier in this Guidance Since the Agency has the right to require that any and all information be submitted and in light of the Agency's current make up, this reviewer knows that the requested information should be submitted and supports the Agency's request for its submission.
# 64 Line "456"	Change 95.0% to 95.0% of target While this reviewer agrees with the commenter, the definition's "(+/- 10%)" should be changed to "(e.g., +/- 10%)" so that the definition does not falsely give the impression that "10%" is the "range.	The document should state that the blend is expressed as a percentage of target. Otherwise the 10% absolute does not make sense.

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# 65 Lines "471-475"	comment 60: lines 471-475 Change this definition to: Stratified Sampling is the process of collecting a representative sample by selecting units deliberately from various identified locations within a lot or batch, or from various phases or periods of a process. Stratified sampling of dosage units specifically targets locations throughout the compression/filling operation that have a higher risk of producing failing results in the finished product uniformity of content; then, random dosage units are selected within these identified locations. This reviewer again suggests that this clearly non-CGMP-compliant definition and the sampling plans tied to it should be deleted from this guidance and the required CGMP-compliant sampling plans substitutes as outlined by this reviewer throughout his review of the Draft and the commenters' submissions that addressed this definition.	To match the technical PQRI definition and to clarify that this sampling strategy is a type of random sampling. Factually, any type of directed-location sampling, such as "stratified sampling" is, cannot be "a type of random sampling." This is the case because, by definition, "random sampling" *means* **sampling** in a manner that each entity in the **population** has an equal chance of being the first member of the **sample**; each remaining entity has an equal chance of being the second member of the **sample**; and so on – subject to the constraint that "each possible **sample** has an equal chance of being selected. Obviously, directed sampling such as *stratified sampling* is not a type of *random sampling*.
# 66 Attachments	Change attachment 2 in two places: Replace 'Adequacy of mix is demonstrated' to 'Adequate Powder Mix'. While this reviewer agrees with the commenter's purpose, this reviewer continues to reject the Attachments as they are now configured.	This change makes Attachment 1 and 2 agree with one another. The attachments do not conform to the clear applicable CGMP **minimums** set forth in **21 CFR Part 211**.
# 67 Attachment 1	Other attributable cause (analytical error) Since, *in a CGMP-compliant manufacturing operation*, "analytical error" would be weeded out before the result values are accepted as valid, "analytical error" should not, except in rare instances, be an "attributable cause" for a problem. Based on this, this reviewer suggests that "analytical error" be replaced with "e.g., operational error, equipment malfunction, processing error, component characteristic change, environmental control excursion, or, rarely, laboratory error."	The commenter did not provide any rationale for this comment. CGMP-compliant laboratory operations, *preferably operating in compliance to ISO 17025*, have internal "critical evaluation of data results" controls that are designed to ensure that only valid result values are reported. However, it is much more common that the true sources of "other attributable" causes are related to component- and manufacturing- related problems.
# 68 Revised Attachment 1 flowchart, line 498	Move box "Assay at least 7 dosage units per each location, weight correct each result" (from line 507) immediately after box that says "Assay 2nd and 3rd blend samples from each location. This reviewer does not support the text in the boxes or the change in placement proposed. *Scientifically sound sampling plans* and *test procedures* (inspection plans) for non-discrete materials ("blends") include sufficient multiple-aliquot assessments of sample uniformity so that the testing, within-sample, between-location and error variance components can be properly assessed without the need to perform any additional testing – hopefully, the commenter is not, *as the commenter seems to be*, advocating the use of less-than-sound inspection practices?	The dosage unit data is generally used as part of the investigation to help correlate blender problems or identify sample bias. As has been established by this reviewer: **1.** Sampling plans proposed for the blend sampling do not conform to the *scientifically sound* and *appropriate requirements* of either **a)** the CGMP regulations or, for that matter, **b)** inspection and analytical science **2.** Active uniformity cannot be validly used to establish what is required, material uniformity for all critical variable factors including, but most certainly not limited to, the active(s) in the material being assessed. **3.** The CGMP regulations clearly require the assessment of the uniformity of the characteristics, not the *biased weight-corrected characteristic* proposed here.

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# 69 Revised Attachment 1 flowchart, line 508	Replace box that says "Assay at least 7 dosage units per each location, weight correct each result" with a box that says "Use dosage units to verify adequacy of powder mix." This reviewer rejects the commenter's proposal along with the original text because the in-process dosage units collected as the Draft suggests cannot be validly used to demonstrate the uniformity of the mix because there is no way to ensure that the dosage-unit samples are from the locations where the alleged blend sample error occurred and the active level is but one, *and not the most critical one in many instances*, of the critical variable factors whose uniformity must be properly assessed in *each batch* (**USA v. Barr Laboratories, Inc., et al.**, Civil Action No. 92-1744, (**812 Federal Supplement 458 (DNJ) 1993**, "Barr Opinion") to establish the uniformity of an in-process drug-product material mix.	Although the results were assayed earlier to help in the blend investigation, now we have identified blend sample error so they must be used to demonstrate uniformity of mix. Factually, because there are steps between the blend sampling and the generation of the dosage units, other than weight, that contribute to the variability in the values observed in the dosage units, the level of active in the dosage units is, at best, a biased estimate of the uniformity of the active in the mix but, because it fails to assess the levels of the other critical components in the formulation cannot validly be used to verify the "adequacy of powder mix." If your manufacturing system includes sampling plans that generate "sample error" or sample bias" of the type described, then your system does not comply with CGMP and the drug products produced by such systems are adulterated and cannot, therefore, be legally offered for sale. Moreover, manufacturers have an absolute legal duty to comply with any clear regulation that the Agency may not legally contravene by publishing a nonconforming guidance document (**Berkovitz v. US, Supreme Court 1988, 486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**). Note: Comment can be disregarded if comment 74 is accepted
# 70 Revised Attachment 2 flowchart	Change STM to SCM and Change MTM to MCM in top 2 boxes This reviewer agrees with the commenter that the terminology should be consistent across the guidance.	TYPOS Note: Comment can be disregarded if comment 74 is accepted.
# 71 Revised Attachment 2 flowchart	In top left box, change first criteria to "last batch was tested using SCM and met SCM acceptance criteria" Provided the procedures and acceptance criteria are changed to be CGMP-compliant, this reviewer does not *per se* object to the commenter's suggestion.	Clarification (because someone will read into this that if it was tested per MCM, but "met SCM acceptance criteria", then SCM is OK now...) Note: Comment can be disregarded if comment 74 is accepted.
# 72 Revised Attachment 2 flowchart	In top right box: remove the first sentence, "Last batch met STM acceptance criteria" Since **the text makes a valid "condition" statement**, the commenter's rationale is anything but clear, and the commenter's rationale does not seem to speak directly to the content of that box in the published draft, this reviewer does not support adopting the commenter's recommendation.	This is not clear as written. Simply, if the last batch was tested using MCM (or started as SCM but had to go to MCM), then the next batch must be tested using MCM. If the last batch was tested per and met SCM, they would not use MCM. Commenter's rationale seems not to match their recommendation.

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# 73 Revised Attachment 2 flowchart	Add document section numbers to a few boxes Provided the draft guidance and the **flow diagrams** provided are revised to be fully conform to the clear applicable CGMP **minimums**, this reviewer is not opposed to adding appropriate document section identifiers to the resultant flow diagrams but would recommend that such labeling be uniformly applied.	To clarify and to connect back to the text If the commenter's intent is to connect the boxes in the flow diagram to the text in the guidance, then all "condition" and "decision" boxes should be labeled. This reviewer also suggests that the more appropriate term to use for "flow chart(s)" or "flowchart(s)" is "flow diagram" because the terms "flow chart' and "flowchart" are usually associated with computer programming and not with diagramming the flow of a process.
# 74 Revised Attachment 2 flowchart	Change box: "You may add results from analysis of remaining samples" to "In addition to the stage 2 results, you may add results from analysis of remaining samples" This reviewer cannot support the commenter's suggestion because it does not match their rationale. If this commenter really intends that one should "use all previously generated data," this reviewer recommends the text be changed to simply state: "You should consider all of the valid results obtained from the testing of all samples."	Clarity. Some have misread that we would not have to use all previously generated data. The use of the word "may" indicates a permissible but not necessarily suggested course of action; in guidance, the word "should" indicates an intended course of action.
# 75 Specifically 80, 82 & 160 and globally wherever the term occurs	Change "Correlate" to "Compare" Except for the times where a statistical contrast is being presented or discussed, this reviewer generally agrees with the commenter here.	"Correlate" has a specific statistical meaning.
# 76 Specifically 108, 115, 143, 146, 167, 172, 238,438 & 441 and globally wherever the term occurs.	Change "Correlation" to "Comparison" Except for the times where a statistical contrast is being presented or discussed, this reviewer generally agrees with the commenter here.	"Correlation" has a specific statistical meaning.
# 77 Line "477"	Replace with term, "Target Strength" This reviewer agrees with the commenter hers.	Clarification

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# 78 **N/A**	Specifically, 1. A dried, milled, mixed (wert or dry) granulation is a "Powder Blend" 2. Technically, bead products are not "powder blends" because they are not "powders." However, *provided the reproducibility of the uniformity of **ALL** the critical variable components in the various beads that comprise the drug product has been established for a given drug product*, then: 1. "Single bead type" drug products can easily fall within the scope of a CGMP-compliant uniformity guidance when the Agency publishes one. 2. *Provided that the manufacturer can establish that the various beads are uniformly distributed in each dosage unit*, it may be possible for a firm to use a CGMP-compliant uniformity guidance when the Agency publishes one for "multiple bead type" drug products.	An exact definition is needed in the document of the term " Powder Blend." Specifically: Clarification is needed concerning whether a wet granulation is included in this definition. Clarification is needed concerning whether the following encapsulated bead products are included in this definition: • Single bead type • Multiple bead type

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.